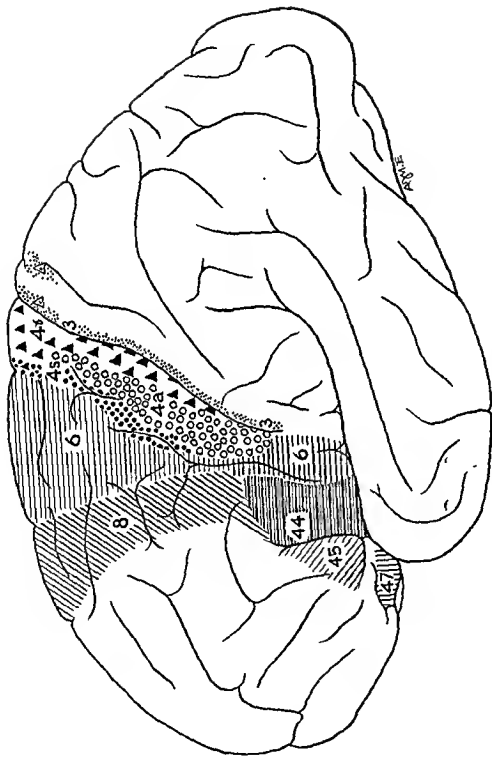# THE PRECENTRAL MOTOR CORTEX

FRONTISPIECE

The precentral motor cortex of man as drawn by von Bonin (see Chapter 11) The symbols △ in area 3 indicate merely the presence of the Betz cells, they do not represent the histological structure of these areas Fissural pattern after Ebertstaller (1890) Compare with figs 4, 6, 9 and 17

THE PRECENTRAL MOTOR CORTEX

Contributors

Charles D. Aring	Marion Hines
Percival Bailey	Margaret A. Kennard
Gerhardt von Bonin	Paul M. Levin
Paul C. Bucy	Warren S. McCulloch
Charles Davison	James L. O'Leary
Theodore C. Erickson	Wilbur K. Smith
John F. Fulton	Sarah S. Tower

A. Earl Walker

Edited by Paul C. Bucy

SECOND EDITION

TO THE MEMORY OF

OTFRID FOERSTER

WHO

STIMULATED THE RECENT RENAISSANCE OF INTEREST IN THE ACTIVITY
OF THE HUMAN CEREBRAL CORTEX

EMPHASIZED THE CORRELATION OF ITS PHYSIOLOGICAL ACTIVITY
WITH ITS MICROSCOPIC STRUCTURE

RECOGNIZED THE IMPORTANCE OF ANIMAL EXPERIMENTATION
FOR THE UNDERSTANDING OF HUMAN PROBLEMS

INSISTED ON THE CONFIRMATION OF THE RESULTS OF
ANIMAL EXPERIMENTATION BY OBSERVATIONS
ON MAN

FOREWORD

ONE OF THE MOST notable contributions to the history of physiology was the discovery of the excitability of the motor area. That the existence of such an area was established independently by two different groups is remarkable: Hughlings Jackson in England concluded through clinical study of cases of focal seizure that a motor area must exist, while Fritsch and Hitzig demonstrated the existence of the excitable cortex by direct stimulation of the forebrain of animals. Since 1870 when these disclosures were made the motor and adjacent areas of sensory and motor function have been intensively studied, but save for Ferrier's and Sherrington's studies on the effects of regional ablation of the motor area and Sherrington's more detailed analysis of its excitable properties, progress during the next sixty years (1870-1930) was less rapid than one might have anticipated. The relations of the motor area to subcortical nuclei, as well as to other regions of the cerebral cortex, were imperfectly understood, largely because existing techniques had failed to bring to light means of analyzing the *organization of the cerebral cortex as a whole.* New techniques were needed— and new horizons.

In 1924 Dusser de Barenne, of Utrecht, visited Sherrington's Laboratory in Oxford with a request that Professor Sherrington help him in applying his strychnine technique in the analysis of the sensory cortex of monkeys. Sherrington willingly gave him the benefit of his wide experience in the handling of monkeys, and Dusser de Barenne inaugurated his now celebrated study on sensory localization in the primate cerebral cortex.

When Dusser de Barenne came to Yale in 1930 he brought with him his new procedures and, with the collaboration of Warren McCulloch and a group of other colleagues, many of them skilled in the techniques of electrical recording, he continued a systematic study of the cerebral cortex and interaction with various subcortical structures, as well as with the interrelations of the various cytoarchitectural regions of the cortex itself. Developments occurred with almost lightning rapidity, and in the ten years in which Dr. Dusser de Barenne was active at Yale one paper followed another, but no opportunity came to summarize the results of his brilliantly conceived research program. Indeed, several years have been required to appreciate the full

significance of what he had accomplished in this brief decade, and had bequeathed to his group of distinguished pupils: Warren McCulloch, Gerhardt von Bonin, Percival Bailey, and Hugh Garol, as well as many others whom he had influenced less directly.

It has fallen to the Neuropsychiatric Institute of the University of Illinois to carry the mantle of Dusser de Barenne, and to all those who concern themselves with the physiology of the nervous system it will be a source of particular satisfaction that through Dr. Paul Bucy's energy and leadership a full-length summary of the latest developments of the physiology of the precentral motor region of the cerebral cortex is now to become available in monographic form. The University of Illinois and its Press are to be congratulated at being able to foster, as well as sponsor, this highly significant contribution to the knowledge and literature of neurology.

J. F. FULTON
Yale University

PREFACE TO THE SECOND EDITION

WHEN the first edition of this monograph was published in 1944 it was not anticipated that another edition would ever appear. It was recognized that the material set forth at that time represented a summary of information in a field in which very active investigation was carrying us forward rapidly. It was hoped that the progress which was being made would soon make that monograph so out-of-date that nothing short of a completely new presentation of the subject of the cerebral cortical mechanism responsible for the control and production of muscular activity would suffice. The popularity of the monograph has exceeded our expectations. Progress has been made but the subject has not yet advanced to the point where a completely new presentation is required. The discovery of the second motor and sensory centers by Adrian (1941), Woolsey (1943, 1944), Woolsey and Wang (1945), and Sugar, Chusid, and French (1948) is one of the most intriguing new developments. As yet, however, our understanding of these is not sufficient to allow us to correlate their activity with the activity of other cortical and subcortical centers. We have decided therefore to re-issue the monograph, making only such alterations as are necessary to eliminate errors and bring the text up-to-date. It is not anticipated that there will ever be another edition of this book. The next requirement will be for a completely new treatment of the subject.

<div style="text-align: right">P.C.B.</div>

ACKNOWLEDGMENTS

CONTRIBUTORS

CHARLES D. ARING, M.D.
Professor of Neurology, University of Cincinnati College of Medicine, Director of the Neurological Service, Cincinnati General Hospital, Cincinnati

PERCIVAL BAILEY, PH.D., M.D.
Professor of Neurology and Neurological Surgery, University of Illinois College of Medicine, Chicago

GERHARDT VON BONIN, M.D.
Professor of Anatomy, University of Illinois College of Medicine, Chicago

PAUL C. BUCY, M.S., M.D.
Professor of Neurology and Neurological Surgery, University of Illinois College of Medicine, Attending Neurologist and Neurological Surgeon, Research and Educational Hospitals, University of Illinois and The Chicago Memorial Hospital, Chicago

CHARLES DAVISON, M.D.
Neuropathologist and Attending Neuropsychiatrist, Montefiore Hospital; Consulting Neuropathologist, Beth Israel Hospital, New York

THEODORE C. ERICKSON, A.M., M.D., M.Sc., PH.D.
Associate Professor of Surgery, University of Wisconsin, Madison, Wisconsin.

JOHN FARQUHAR FULTON, M.A., PH.D., M.D., LL.D., D.Sc.
Sterling Professor of Physiology, Yale University School of Medicine, New Haven

MARION HINES, PH.D.
Professor of Experimental Anatomy and Research Assistant in Physical Medicine, Emory University, Atlanta

MARGARET A. KENNARD, M.D.
Associate Professor of Experimental Surgery, University of Oregon Medical School, Portland

PAUL M. LEVIN, M.D.
Assistant Professor of Neuropsychiatry, Southwestern Medical College, and Attending Neurologist Texas Children's Hospital, Dallas

WARREN STURGIS MCCULLOCH, A.M., M.D.
Professor of Psychiatry, University of Illinois College of Medicine, Chicago

JAMES L. O'LEARY, PH.D., M.D.
Professor of Neurology, Washington University School of Medicine, St. Louis

WILBUR K. SMITH, M.D.
Associate Professor of Anatomy, University of Rochester School of Medicine and Dentistry, Rochester N Y

SARAH S. TOWER, PH.D., M.D.
Instructor in Psychiatry, The Johns Hopkins University, Baltimore

A. EARL WALKER, M.D.
Professor of Neurological Surgery, The Johns Hopkins University, Neuro-surgeon-in-Chief, The Johns Hopkins Hospital, Baltimore

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Chapter I

INTRODUCTION

Paul C. Bucy, M.S., M.D.

Professor of Neurology and Neurological Surgery
University of Illinois College of Medicine

and

Attending Neurologist and Neurological Surgeon
Illinois Research and Educational Hospitals
and The Chicago Memorial Hospital
Chicago

INTRODUCTION

KNOWLEDGE OF THE FUNCTIONAL ACTIVITY of the cerebral cortex and its relation to the complex structure found there has lagged and is still lagging far behind our knowledge concerning the rest of the nervous system. Only the basal ganglia share this dungeon of ignorance with the cortex. Recent years have seen some advance with regard to two areas of the cortex—the area striata and the precentral region. Our familiarity with the structure, connections, and functions of the striate area of the occipital lobe has been achieved principally by the researches of Polyak, Brouwer, and Holmes. The available information in this field is now being collected and published by Polyak.

Renewed interest in the precentral region was stimulated by the observations made by Otfrid Foerster on the electrical excitability of the human cerebral cortex. The recent clarification by experimental means of the many problems concerned with this interesting phase of cerebral physiology was begun in the laboratories of Dr. John F. Fulton at Yale University. From that focus, interest spread in ever widening circles to many of the laboratories and clinics of this country.

It can not be assumed that all the mysteries of the precentral region have now been laid bare. But it does seem that we have now reached a stage in our investigations in this field where we can advantageously bring together in one volume the results of the now widely divergent researches. In preparing this volume we have been fortunate in having the willing and enthusiastic collaboration of the people who have done much of the original investigation.

Several problems have confronted us. The principal of these is concerned with what is to be included in this volume—with what is meant by the *Precentral Motor Cortex*. Obviously the precentral region does not function independently of the rest of the cortex, and if those other parts of the cortex in any way concerned with the activity of the precentral region were to be included in this discussion the volume would have to encompass the entire cerebral cortex

The editor regards the precentral motor cortex as the principal efferent or effector cerebral cortical mechanism by which the brain expresses its activity through the skeletal musculature. The portion of the precentral region principally so engaged is the cytoarchitectonic areas 4, 6, and 44. These areas and their subdivisions have another characteristic in common. They are the part of the cortex in which the thalamocortical projections from the ventrolateral nuclei of the thalamus terminate.

3

Although area 8, the frontal motor eye fields, was not included in the term *precentral motor cortex*, it seemed well to include a discussion of it in the volume for two reasons. It, too, is concerned with the voluntary innervation of striated musculature, the extra-ocular muscles, and it functions as a suppressor area having many of the same characteristics as area 4s. Areas 18 and 19 were not included, although they, too, innervate the ocular musculature and although area 19 is a suppressor area, because their control over the ocular muscles seems to be more of a reflex automatic activity than of a conscious voluntary control, and because they are not precentral.

Brief consideration is also given to the anterior limbic area, which occupies the anterior part of the cingular gyrus, and the area orbitalis agranularis. Both of these lie in the frontal lobe and, although not directly precentral, bear an obvious spatial as well as functional and anatomical relationship to the precentral motor cortex. The anterior limbic area is an important part of the suppressor system and closely related to areas 4s and 8 (cf. Chapter VIII). The agranular area on the orbital surface is also an important part of the frontal efferent or effector system. It appears to be primarily concerned with the cortical control of respiration and possibly other vegetative functions, just as the precentral motor cortex is concerned with the cortical control of skeletal musculature and of such vegetative functions as vasomotor and gastrointestinal activity (cf. Chapter XI).

Within the precentral motor cortex we have been at considerable pains to achieve a subdivision which was of anatomical and functional significance and a terminology which was as much as possible in keeping with what we believe to be current usage. On this basis we have designated the area gigantopyramidalis as area 4γ (this is area FAγ of von Economo and Koskinas) The precentral suppressor strip of Marion Hines was designated as "the strip" by Hines and, in keeping with that, as "area 4s" by Dusser de Barenne, McCulloch, and their co-workers (fig. 101, p 267). This usage by those who have done the most to elucidate this area is respected in the present volume, although the editor admits to more than a little dissatisfaction with the term 4s, which implies a more intimate relationship with area 4, as compared to area 6, than the facts fully justify.

We are at a considerable disadvantage in studying the human brain because it differs from the subhuman primate brains in that it has a new area, essentially devoid of gigantic pyramidal cells of Betz in the fifth cortical layer, between the area gigantopyramidalis and the strip 4s Our knowledge of the various electrical characteristics and functional activities of this new area, found only in the human brain, is so limited as to be of no use to us in classifying this area. Microscopically it does not differ ma-

terially from area 6. although it differs decidedly from area 4γ behind it and area 4s in front. Having committed ourselves to calling the precentral suppressor strip 4s, it seemed best to designate this new area as 4a, and thus include it with the other areas 4. rather than to give it a separate designation or to label it as a subdivision of area 6. Our area 4a is comparable to area FA of von Economo and Koskinas and to area 6aα as drawn on the maps of the human cortex by the Vogts (fig. 3a, p. 12. and fig. 99, p. 264). The microscopical characteristics of these areas are carefully defined in Chapter II. In view of these facts and our limited knowledge concerning the physiological activity of the human area 4 and its relation to the experimental characteristics of areas 4 and 4s in animals, the actual terminology is of secondary importance. Furthermore, our designation of this area as 4a in the numerical scheme of terminology is in keeping with the designation of this same area as FA by von Economo and Koskinas.

The agranular area immediately anterior to area 4s has been designated as 6. Since we have been unable to convince ourselves that there are any significant subdivisions, the designations 6aα and 6aβ of the Vogts have been abandoned.

The most anteroventral part of the precentral region or subsector was designated area 6b by the Vogts (fig. 99, p. 264). However, as is pointed out in Chapter II. its microscopical appearance differs considerably from that of area 6a of the Vogts. Whereas area 6a is definitely agranular, area 6b contains a "faint but nonetheless distinct inner granular layer" which has caused all investigators to designate it as dysgranular. Furthermore, it does not respond on electrical excitation like area 6a (cf. Chapters IX and XI), and when studied by Dusser de Barenne's technique of physiological neuronography (Dusser de Barenne. McCulloch, and Ogawa, 1938) it lacks the characteristics of area 6a. It is thus obvious that the terminology "6a" and "6b," which implies a similarity between the two areas, is misleading. Accordingly, at the suggestion of Dr. Percival Bailey, we have adopted "area 44" as the designation for area 6b of the Vogts. This terminology implies a homology between area 6b (Vogts; fig. 100, p. 266) in the monkey and area 44 of Brodmann (fig. 2a, p. 11) and area FCBm of von Economo and Koskinas (fig. 3a, p. 12) in man which is thoroughly supported by microscopic examination (see Chapter II). We have also dropped the "a" from "area 6a," and this agranular frontal cortex lying anterior to area 4s now becomes area 6, returning again to the original terminology of Brodmann. However, it should be noted that he did not differentiate between area 6 and area 44 in the lower precentral region of the monkey.

Throughout this monograph we have attempted to use the terminology for the thalamic nuclei which was employed by Walker in his monograph

(see Chapter IV, and fig. 105, pp. 284-285). Thus, that portion of the lateral nuclear mass which projects onto the precentral motor cortex is designated as the ventrolateral nucleus. This is the nucleus in which the cerebellar fibers passing through the brachium conjunctivum (Chapter X), and probably fibers from the lenticular nucleus, terminate. The ventroposterior nucleus, composed of the ventroposterolateral and -medial nuclei, lying in the posterior part of the lateral nucleus mass is the recipient of impulses over the spinothalamic tract, the medial lemniscus, and the trigeminothalamic pathway, and it projects to the postcentral gyrus.

The authors who have contributed to this monograph are familiar with their subjects through firsthand experience. Each author is pre-eminent in the field which he has presented. Accordingly, the editor has not seen fit to quarrel with any of them about the stated facts or the expressed opinions, but has been content to insist only that they express themselves as clearly as possible and explain their opinions and show their evidence as fully as space permits. That there are differences of opinion and disagreements between various authors in this monograph disturbs the editor not at all. It could not be otherwise among a group of intelligent, industrious scientists who are at the moment busily engaged in determining and interpreting the facts in this active field of neurological investigation. Complete agreement, or one-sided dogmatic statements on controversial issues, would not represent the true state of knowledge and opinion in this field at this time.

At the suggestion of Dr. Warren S. McCulloch and Dr. Gerhardt von Bonin, there is included in this monograph a translation of the excellent though old, unfamiliar, and long-neglected paper by Bubnoff and Heidenhain (1881) on the physiology of the precentral cortex. This paper deals primarily with the electrical excitability of this region. Although some of its material has been publicized by other investigators, it is reproduced here in its entirety for several reasons: first, because in its original form it has not been readily available to all readers; second, because it is unfamiliar even to many who work intensively in this field; third, because its authors have not received just credit for their work; and fourth, most important of all, because it sets forth the facts clearly and concisely. The excellent translation has been prepared by Drs. Bonin and McCulloch.

This volume does not represent a final expression of fact and opinion on the precentral motor cortex. It is but a summing up of the important findings to date, so that those who would know what has thus far been accomplished and those who would carry on from here may have available a coherent summary and a guide to the literature for their ready acquisition of knowledge at a saving of their time.

Chapter II

ARCHITECTURE OF THE PRECENTRAL MOTOR CORTEX AND SOME ADJACENT AREAS

Gerhardt von Bonin, M.D.

Professor of Anatomy
University of Illinois College of Medicine
Chicago

OUTLINE OF CHAPTER II

The Architecture

Prefatory Note

It is our belief that the usual omission of layer IV from the precentral agranular cortex is conducive to erroneous thinking. The importance of any structure resides in its function. The thalamocortical afferents terminate in the outer stripe of Baillarger. The region containing this stripe has been called layer IV in the postcentral but the lower part of layer III in the precentral cortex It should, however, be referred to as layer IV in all areas of the neocortex, and we have done so in this chapter.—Bonin and Bucy.

THE ARCHITECTURE

EACH THALAMIC NUCLEUS which is connected with the cerebral cortex sends radiations only to a circumscribed part of the cortex (cf. Chapter IV). It is thus possible to define a cortical "sector" by the thalamic nucleus from which it receives impulses It is true that certain parts of the cortex do not receive any radiations from the thalamus. Some of them are in such close functional relation with cortical areas receiving thalamic radiations that they form a natural unit with them. The parastriate area, for example, should be included with the striate area in the visual or occipital "region." Other parts, as perhaps areas 21 and 22, form a separate region by the very fact that they are devoid of thalamic radiations. Pursuing this thought, it is then possible to define a "central sector" by its property of receiving thalamic radiations from the lateral nuclear mass, a "frontal sector" by its radiations from the dorsomedial nucleus of the thalamus, and a "limbic sector" by its radiation from the anterior nucleus. It is further possible to subdivide the central sector into several parts. A precentral subsector receives radiations from the ventrolateral nucleus. These radiations conduct impulses originating in the cerebellar cortex and, according to Papez and Stotler (1940) and to Papez (1940b), in the pallidum. There follows occipitad a postcentral subsector connected with the posteroventral nucleus which receives the medial lemniscus and the spinothalamic tract, and a third parietal subsector receiving its radiations from the pulvinar. The detailed organization of the postcentral and parietal subsectors is not clear at present but need not concern us in this monograph.

The precentral motor cortex proper can then be defined as the precentral subsector. Its description forms the bulk of this chapter. In close functional connection with it are three other areas: (1) The cortical area just in front of the precentral motor cortex, which Brodmann (1909) called 8 (fig. 2) and von Economo and Koskinas (1925) FC (fig. 3). It is the frontal suppressor area (cf. Chapter VIII) and the frontal oculo-motor area (cf. Chapter XII). (2) The area orbitalis agranularis, area 47 of Brodmann and FFa of von Economo and Koskinas. It is concerned with respiratory movements (Bailey and Sweet, 1940). (3) Finally the anterior limbic area, Brodmann's 24, von Economo and Koskinas' LA and Rose's area infraradiata. It is the "limbic suppressor area." A brief description of these areas will be given in the fourth part of this chapter. The "second motor area" on the infraparietal plane (the superior wall of the Sylvian fissure in the frontal and parietal region), which Sugar, Chusid, and French

(1948) discovered in the macaque and which is also present in the chimpanzee, doubtless also has important functional connections with the precentral motor cortex. It has not received consideration here because of the lack of adequate and detailed information at this time.

The following nomenclature will be used: The term "sector" defines a part of the cortex, characterized by its thalamocortical connections. The term "subsector" and, for the sake of variety, the term "cortex," in such combinations as "precentral motor cortex," will be used much more frequently. Its definition should be clear from the foregoing discussion. The term "area" designates a cytoarchitectural entity. The term "field" is applied to a functional subdivision of an area, e.g., to the "leg field," etc. A group of functionally related areas is called a "region."

It is assumed that the reader is familiar with the architecture of the cortex. It has been ably set forth by such authors as Lorente de Nó (1943), von Economo and Koskinas (1925; cf. fig. 3), O. and C. Vogt (1919), Cajal (1911), Brodmann (1909, 1914, 1925; cf. fig. 2), and Campbell (1905; cf fig. 1), to mention but a few.

Some points of cortical architecture may be summed up thus:

Afferent fibers from the thalamus form an axonal plexus in the outer stripe of Baillarger, situated in what cytoarchitecturally is known as the fourth layer and in many areas spilling over into layer *iiic*. Associational and commissural fibers break up in the stripe of Kaes-Bechterew in layers *ii* and *iiia* and in the inner stripe of Baillarger in layers *vc* and *vi*.
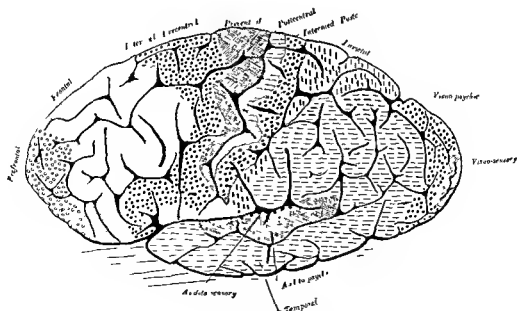

Fig 1—Map of the lateral surface of the human cortex. After A W Campbell (1905), by permission of The Macmillan Co., N Y
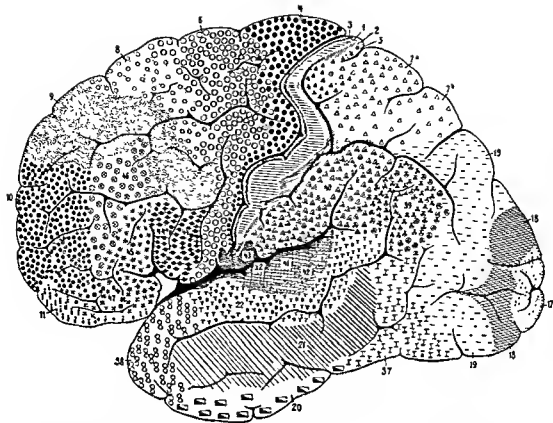
Fig 2a.—Map of the lateral surface of the human cortex. After K. Brodmann (1914, Bd 11, I Teil), some lettering redrawn. Note changes from his earlier map (1909). 7 divided into 7a and 7b, 44 into 44 and 44a, 52 inserted.
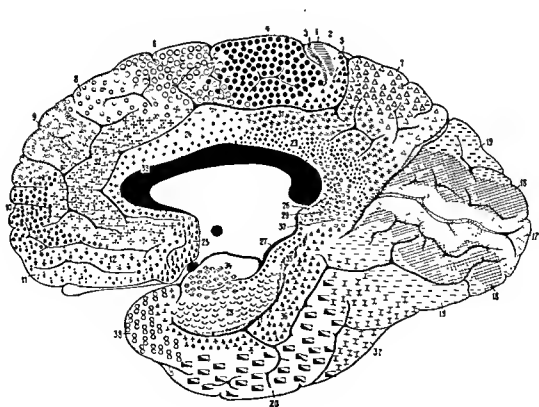

Fig 2b.—Map of the medial surface of the human cortex. After K. Brodmann (1914, Bd 11, I. Teil).

FIG 3a—Map of the lateral surface of the human cortex After von Economo and Koskinas (1925) Frontal and parietal opercula are pushed up to show island of Reil

FIG 3b—Map of the medial surface of the human cortex After von Economo and Koskinas (1925)

Corticifugal fibers arise from pyramidal cells in layer *vb*, such as the giant Betz cells in the motor cortex and the solitary cells of Meynert in the visual cortex. These "efferent" cells can only indirectly be influenced by incoming impulses via "internuncial" neurons.

Analysis of the motor cortex is impeded by the fact that the definitions of cytoarchitecture are too narrow. They are based on cell size, cell density, and, to a lesser degree, on cell shape. Cytoarchitecture fails to take into account the axonal (or dendritic) plexuses. Yet it so happens that within the precentral subsector that stratum which contains the outer stripe of Baillarger does not differ from the other strata in respect to cell size or cell density. This cortex is therefore frequently described as "agranular," a statement usually interpreted to mean that the fourth layer is absent. As we shall see, however, an outer stripe of Baillarger, i.e., an axonal plexus of specific afferents, is present. A stratum which has the function elsewhere subserved by a fourth layer exists, therefore, in the motor cortex as well as anywhere else. Many difficulties vanish if the definitions of cortical layers are cast in broader terms.

SUBHUMAN PRIMATES

It is doubtful whether the definition of the precentral subsector just given is workable for all classes of mammals. In the rat, at any rate, Lashley (1941) found "no evidence that any fibers go from the ventral nucleus[1] to the Regio precentralis of Brodmann and Rose." Krieg (1947) similarly states that for the rat there is "no evidence that area 4 receives projections from any thalamic nucleus." In the cat, on the other hand, Waller (1940) found fibers from the "ventral anterior nucleus[1]" to reach the motor cortex.

The sketch to be given on the ensuing pages, however, aims at establishing the main trend of anthropogenesis only during the primate stage. Even within this group it deliberately concentrates on but a few species. Some of these are laboratory animals, while others are alluded to because they illustrate interesting phylogenetic steps. A review of the motor cortex, in the narrower sense of the term, was given by E. Huber (1934).
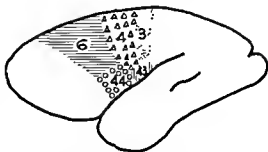
Fig 4—The precentral motor cortex of the galago lemur. Compare with figs 6, 8, 9, 17, and frontis-piece

[1] The "ventral nucleus" of Lashley (1910) and Waller (1910) forms part of the lateral nuclear mass of Walker

We are sometimes forced to establish homologies indirectly. It is known of numerous animals that the precentral motor cortex shows a very characteristic cytoarchitecture, and it is by this criterion, as well as by physiological experiments, that we distinguish the motor cortex of those animals in which the thalamic radiations are not yet known

Lemurs

In the Galago (fig. 4), a small lorisiform lemur with an almost lissencephalic brain, the precentral motor cortex can be recognized by its cytoarchitecture (fig 5) an account of which was given by Zuckerman and Fulton (1941) and by Bonin (1945) Bonin subdivided the precentral motor cortex of the Galago into three areas (cf. fig. 4) Two of these are
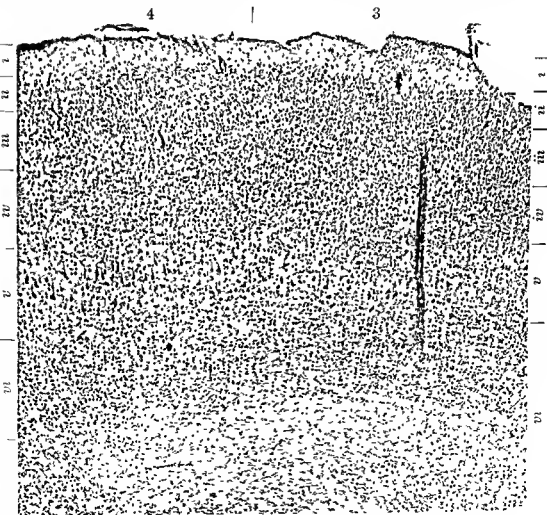
Fig. 5 —The motor cortex of galago Own preparation, left, area 4, right, area 3 Compare with figs 7, 10 12 18 29 30, and 33

agranular while the third shows a thin inner granular layer. The posterior part of the agranular cortex contains rather large pyramidal cells in the fifth layer which nobody will hesitate to identify as the giant cells of Betz. Thus, the presence or absence of Betz cells allows us to define two areas corresponding to Brodmann's areas 4 and 6 as described by that author (1909 and 1912) in *Lemur macaco*, and by Mott and Kelley (1908) in *Lemur brunneus, mongoz*, and *catta*. The division into a motor cortex proper, and, to introduce a term coined by Herrick (1926) and taken up by Fulton (1936), a premotor cortex, is clearer in primates than in any other mammalian class studied thus far. The third (dysgranular) area occupies the anteroventral part of the precentral subsector, and by virtue of its topological relations has to be called area 44.

Platyrrhine Monkeys

Hapale. The cortex of Hapale (Peden and Bonin, 1947) closely resembles that of Galago and alouatta in its cytoarchitecture. Peden and Bonin recognized areas FA, FB, FCBm, and FF which are, in the nomenclature employed here, areas 4, 6, 44, and 47 respectively.

Alouatta (fig. 7) — The brain of alouatta was briefly mentioned by C. and O. Vogt (1936). It is one of the most primitive gyrencephalic brains of which we have information about the motor area. From the figure given by the Vogts it appears that the Betz cells are comparatively small (fig. 7) and that the posterior margin of area 4 does not coincide with the central sulcus, but runs for a long stretch well in front of it (fig. 6).

Fig. 6—Outline of the hemisphere of alouatta. Redrawn after C. & O. Vogt (1936, fig. 56). *cc*, central sulcus. 4, area 4. Compare with figs. 4, 8, 9, 17, and frontispiece.

Cebus (fig. 8) — The cortex of the cebus was described by Bonin (1938a), but in that account the definition of the precentral cortex adopted here was not clearly grasped. A comparison with other forms, particularly with the macaque, justifies the statement that the precentral motor cortex of the cebus consists of three areas. In the terminology of the paper just cited these are the area gigantopyramidalis, homologous to Brodmann's area 4, the area precentralis simplex, homologous to 6a of C. and O. Vogt (1919), and the area fronto-opercularis, homologous to 6b of C. and O. Vogt. The posterior boundary of the precentral motor cortex coincides largely but not completely with the central sulcus.

The histological details differ little from those found in the macaque. They were described in detail in the original publication.
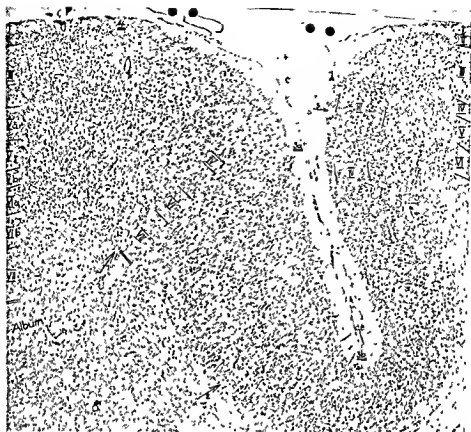
FIG 7—Motor cortex of alouatta After C & O Vogt (1936 fig 57) Section through the central sulcus, area 4 to the left Note that almost the whole of the anterior wall of the central sulcus is taken up by area 3 Compare with figs 5, 10, 18, and 29
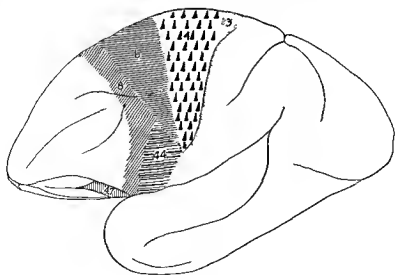

FIG 8—The motor cortex of cebus Redrawn after Bonin (1938a) Compare with figs. 4, 6 9 17 and frontispiece

Catarrhine Monkeys

Macaque (fig. 9)—In the macaque, the precentral subsector can be defined by its thalamocortical connections, well known from the work of Walker (1938a), Le Gros Clark (1932b), and various others. The cytoarchitecture of the neocortex of the macaque was described recently by Bonin and Bailey (1947), and its myeloarchitecture was analyzed by Mauss (1908). Further data on the motor area were given by Mellus (1905), Nañagas (1923). Lassek (1941b), and others. The motor area proper (fig. 10) shows the same features as that of other primates. Just as in the galago, the giant cells of Betz are not restricted to area 4, but are also found in the postcentral and even in the parietal cortex (Levin and Bradford, 1938; cf also Chapter V). From the writer's limited experience it would appear as though the macaque were unique in the number of Betz cells found in the parietal lobe. Neither the cebus nor the mangabee (cercocebus), one brain of which could be examined in a sagittal series, nor even the chimpanzee show any giant cells in the parietal cortex, and in man they are limited to areas PA and PEγ of von Economo and Koskinas. Within area 4, the giant cells show what Brodmann called a multilaminar arrangement. In the precentral subsector of one hemisphere Lassek (1941b) counted 18,845 Betz cells.

Close to the anterior border of area 4 there is in some brains a narrow zone containing conspicuously large cells in layer IIIa (fig. 11). It corre-
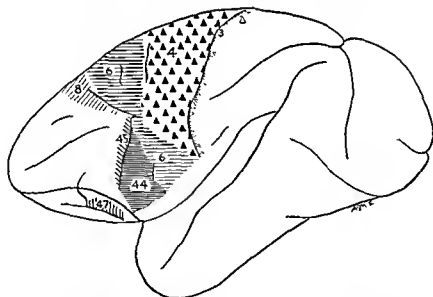
Fig 9—The precentral motor cortex of the macaque For numbers of areas, see text The symbol △ in area 3 indicates merely the presence of Betz cells there, not the histological structure of this area Compare with figs 4, 6, 8, 17, and frontispiece.

sponds in its position to area 4s, but is inconstant. Hence it has been
omitted by Bonin and Bailey (1947).

The remainder of the precentral motor cortex (figs. 12 and 13; cf. fig 9)
was divided by C and O. Vogt (1919) into areas 6a and 6b Their area
6a we shall call area 6. It is agranular. Its anterior part, which the Vogts
labelled 6aβ has a narrower second layer and narrower layer IIIc + V, and
a clearer distinction between layers *va* and *vb* than its posterior part which
they labelled 6aα (cf Vogt's photographs, 1919). However, these differ-
ences are so tenuous that they have not been utilized here. Furthermore,
the Vogts applied the term 6aα to areas which are not homologous in man
and monkey, since 6aα is occipital to area 4s in man, and frontal to area 4s
in the monkey. Their area 6b will be called area 44 in this monograph. It
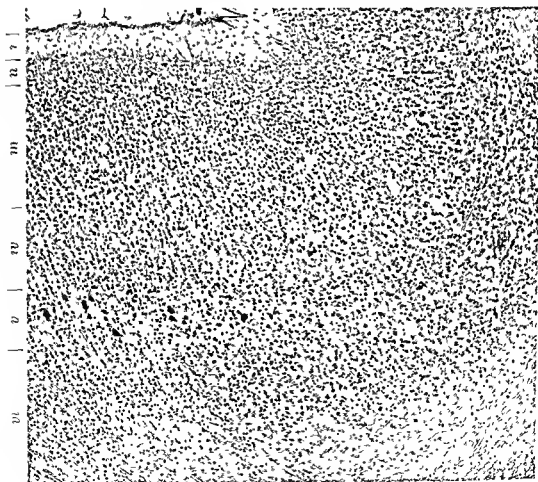
Fig. 10 —Area 4 of the macaque, in the depth of the central sulcus Section prepared
by John Hamilton for the late Dr Dusser de Barenne Note transition between area 4 (left)
and area 3 (right) Magnification about 45 1 Compare with figs 5, 7, 18, 29, and 30

contains a faint but nonetheless distinct inner granular layer. It is, in the nomenclature of the Vogts and their collaborators, dysgranular, not agranular. It also shows a narrower third layer than area 6. Its fifth layer can be divided into two sublayers, of which the lower one is poorer in cells. The sixth layer is much narrower in area 44 than in area 6. The Vogts subdivided their area 6b once more into 6bα and 6bβ. Dusser de Barenne, McCulloch, and Ogawa (1938) were unable, however, to confirm this subdivision by the method of physiological neuronography, and it has not been retained here. As will be fully explained in Chapter VIII, the leg and arm fields of the precentral motor cortex consist of areas 4, 4s, and 6, while the face field consists of areas 4, 4s, 6, and 44.
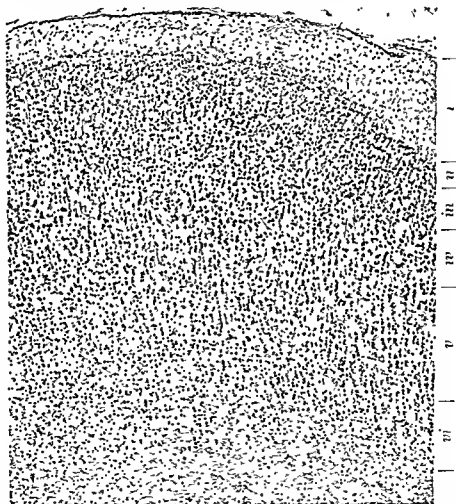
Fig. 11—Area 4s of the macaque. Section prepared by John Hamilton for the late Dr. Dusser de Barenne. Note the large pyramidal cells in layer v, to the left. Magnification about 45:1. Compare with figs. 19 and 32, see text pp. 17–18

The fissural pattern of the brain of the macaque (fig. 14) has been surveyed by Mettler (1933) and by Bonin and Bailey (1947). The account to be given here is based on the study of brains (given to the writer by Dr. I. Schour) which had been hardened in situ and removed after several weeks, and of the brains in the collection of the Illinois Neuropsychiatric Institute which had been used by Dusser de Barenne and McCulloch for their experiments. Altogether, about 25 brains were available.

The most conspicuous landmark of the precentral subsector is the central sulcus (*ce*). The term "sulcus of Rolando" is probably used almost as frequently as its "official" name. It runs from a point close to the dorsal margin of the hemisphere in a ventrofrontal direction to a point close to

Fig. 12.—Area 6 of the macaque. Section prepared by John Hamilton for the late Dr Dusser de Barenne. Note the columns of cells. Magnification about 45 : 1. Compare with fig 33

the Sylvian fissure. Encephalometric data pertaining to the central sulcus
are given in Table I. The rolandic index is obtained by measuring the dis-
tance of the (ideal) endpoint of the central sulcus from both frontal
and occipital poles and expressing the former quantity as a percentage of
the latter. For the mesial index the distances of the upper endpoint at the
dorsal margin of the hemisphere and for the lateral index the distances of
the lower endpoint at the Sylvian fissure are taken. The technique has
recently been discussed in detail by Bonin (1941). The central sulcus is
generally S-shaped and shows a distinct curve convex frontad near its
ventral end, where it bends variably backward. The lower end of the sulcus
may form a pronounced hook or may show no more than a slight occipitad

FIG 13—Area 44 of the macaque Section prepared by John Hamilton for the late Dr
Dusser de Barenne Note the trace of the inner granular layer, and the large pyramidal cells
immediately below and above that layer Magnification about 45 1. Compare with figs
20 and 34

deviation from the course of the main part of the sulcus. Hines (1933) states that the central sulcus may occasionally cut into the dorsal margin and run for a short way on the medial side of the hemisphere We have never observed this. The central sulcus is fairly deep in its whole course There are no submerged gyri within it in any of the macaque brains which the writer has been able to examine.

The lateral, or Sylvian, fissure (*la*) forms the lower boundary of the precentral motor cortex and should for that reason be mentioned, although its greatest part lies outside this subsector. After it has emerged onto the lateral side of the brain it takes a sweeping course occipitad and slightly upward. It does not give off any side branches cutting into the precentral motor cortex.

The arcuate sulcus consists of two rami, a superior (*rsa*) and an inferior one (*ria*). Broca (1888) called the sulcus "sillon courbe frontal" According to Marchand (1893), Mingazzini introduced the Latin translation arcuate sulcus into the literature. Kukenthal and Ziehen (1895) called the rami *q* and *q'*, and used the symbol *q''* for the short backward continuation of the superior ramus which is sometimes present.

The superior precentral sulcus (*prcs*) is generally a small dimple a few millimeters long. It was designated as *z* by Kukenthal and Ziehen, and was shown, but not labelled, by Gromier (1874). According to Kukenthal
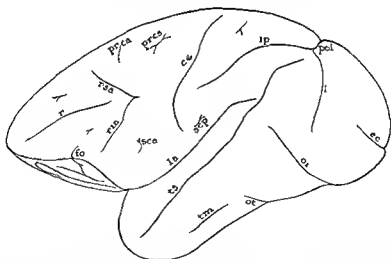
Fig 14 —The fissural pattern of the lateral side of the cortex of the macaque Abbreviations *ce*, s centralis (of Rolando), *ce*, s calcarinus externus, *fo*, s fronto-orbitalis, *ip*, s intraparietalis, *l*, s lunatus, *la*, lateral fissure (of Sylvius); *oi*, s occipitalis inferior, *ot*, s occipito-temporalis, *pol*, incisura parieto-occipitalis lateralis, *prca*, s praecentralis anterior, *prcs*, s praecentralis superior, *r*, s rectus, *ria*, ramus inferior, *s* arcuatus, *rsa*, ramus superior, *s arcuatus*, *sca*, s subcentralis anterior, *scp*, s subcentralis posterior, *tm*, s temporalis medius, *ts*, s temporalis superior

Table I
ROLANDIC INDICES

A. After Cunningham (1892)

	Mesial	Lateral
Man (82)*	53 3	43 3
Chimpanzee (4)	55 9	49 2
Macaque (5)	50 0	40 3

B. After Connolly (1936)

		Mesial	Lateral
Man	White (10)*	57 6	40 5
	Negro (37)	57 1	39 3
	Malay (10)	60 0	38 7
Chimpanzee (5)		61 8	36 3

C. After Bonin (1941)

	Mesial	Lateral
Man (25)*	58 4 ± 68	41 0 ± 41
Chimpanzee (10)	59 05 ± 81	36 1 ± 1 14
Macaque (11)	53 8 ± 51	38 2 ± 75

Test of Significance of Bonin's Figures†

	Man	Chimpanzee	Macaque
Man		0	+
Chimpanzee	+		+
Macaque	0	0	

* Numbers in parenthesis indicate the number of cerebral hemispheres examined
† Upper right mesial Rolandic index, lower left lateral Rolandic index

and Ziehen, it has a transverse position in the brain of the macaque, while it is generally sagittal in cynocephalus. It is this sulcus, and not the one labelled f_1 by Mettler which Kukenthal and Ziehen call the superior precentral. The anterior precentral sulcus (*prca*) is a small dimple in front of *prcs* which Kükenthal and Ziehen labelled "z". Cunningham called the same sulcus the first frontal. Still further in front, forming almost a continuation of the superior ramus of the arcuate, Kukenthal and Ziehen showed a short transverse furrow which they labelled *J*. A small dimple on the frontal operculum was given the letter *N* by Kükenthal and Ziehen, and called subcentralis anterior by all other authors.

The posterior boundary of the precentral subsector coincides with the central sulcus. The ventral continuation of this sulcus cuts into area 43 (PFC of Bonin and Bailey). The map of C. and O. Vogt (1919) and Bucy's (1935b) maps D and G show area 3 to extend in front of the central sulcus. Bonin and Bailey (1947) believe this to be an erroneous interpretation. The anterior boundary coincides fairly closely, as Bucy's figures indicate, with the arcuate sulcus. However, the relation between this sulcus and the areal boundary is more unstable than that of the central sulcus. The border between area 44 and area 6 is marked by the sulcus subcentralis anterior.
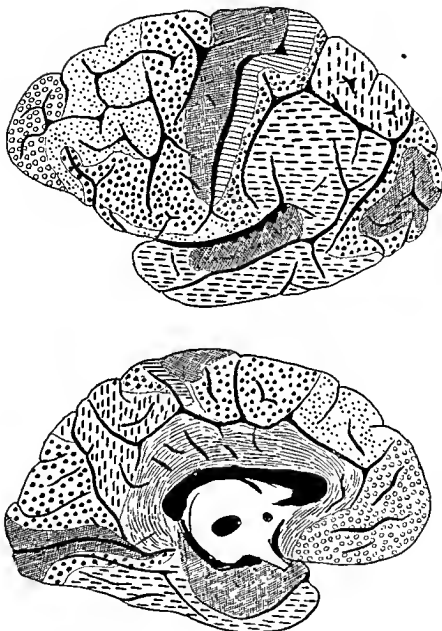
FIG 15 —Map of the cortex of the chimpanzee After A W Campbell (1905), by permission of The Macmillan Co , N Y

Within the precentral subsector, area 4s when present is found close to the superior precentral sulcus.

Anthropoids

Chimpanzee—In the chimpanzee, thalamocortical connections are well known through the work of Walker (1938b). The cytoarchitecture of the cortex was studied by Campbell (1905; fig. 15). His map is unsatisfactory, for he fails to differentiate as many areas as have been identified subsequently, either anatomically in closely related forms or physiologically in the chimpanzee itself. Mauss (1912) gave a myeloarchitectural map of the orang, (fig. 16) which, for want of a better map, may be used for the chimpanzee, since the brains of these two anthropoids are very similar. Some parts of the chimpanzee's brain have recently been worked out in greater detail. Strasburger (1937) gave a detailed myeloarchitectural study of the frontal lobe, and Gerhardt (1938) studied the parietal lobe in the same way. Both papers emerged from the laboratory of C. and O. Vogt, and the criticism that can be leveled against the extreme parcellation of these authors applies with equal force to the results of their co-workers. Kreht (1936a), also under the guidance of O. Vogt, published a cytoarchitectural study of the third frontal convolution.

The description of the cytoarchitecture of the chimpanzee's precentral motor cortex is mainly based on studies by Bailey, Bonin, and McCulloch to be published shortly.

The chimpanzee (fig. 17) shows the same areas within the precentral motor cortex that were found in the macaque (4, 6, and 44). The most posterior of these is area 4. However, if Brodmann's definition of area 4 as the area gigantopyramidalis is adhered to, then the posterior border of this area is not identical with that of the agranular precentral motor cortex. In the chimpanzee there is a narrow strip of agranular cortex between the granular postcentral area 3 and the gigantopyramidal cortex of area 4 (fig. 18). Thus, in the class of primates the transition between area 4 and area 3 shows one of three variants. There may be no transitional zone, or the giant cells may crowd into area 3, as in lemur, cebus, and macaque, and in man, or finally, the giant cells may stop short of the boundary and thus leave a strip of simple agranular cortex, as in the chimpanzee. Area 4 does not differ much in its cytoarchitecture from the homologous area in the macaque. The relative size of the Betz cells, however, appears to be greater than in the monkey. The giant cells are arranged in irregular clusters. No Betz cells were observed in the postcentral or the parietal subsector.

Between areas 4 and 6 there is a narrow strip which contains large cells in layer *iv* (fig. 19). It appears to correspond to the precentral sup-
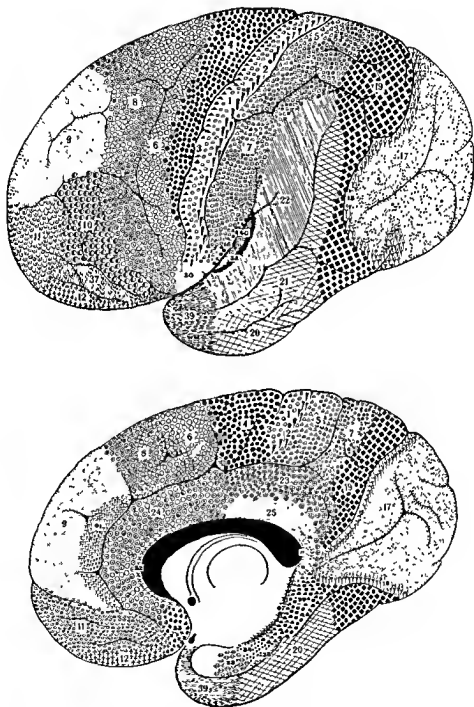
Fig 16—Myeloarchitectural map of the cortex of the orang After Th Mauss (1912)

pressor area (4s), but it is even less conspicuous than the similar strip in the macaque's brain.

Area 6 shows a slight columnization and its cells are smaller than those of area 4.

The dysgranular cortex of area 44 (fig. 20) in the anteroventral part of the precentral subsector can be easily recognized by the faint but unmistakable inner granular layer. Layers *iii* and *v* lend themselves to divisions into sublayers much more readily than do the other areas of the precentral motor cortex, and both layers contain conspicuously large cells. The homology with area 44 of the macaque is perfectly obvious. Kreht (1936a) and Strasburger (1937) subdivided 44 into two areas which they called 56 and 57. Whether these are homologous to 6bα and 6bβ, which the *Vogts recognized in other primates (cercopithecus)*, must be left undecided.

The fissures of the chimpanzee's brain (fig. 21) have been the object of numerous studies, most of which are listed in a recent paper by Walker
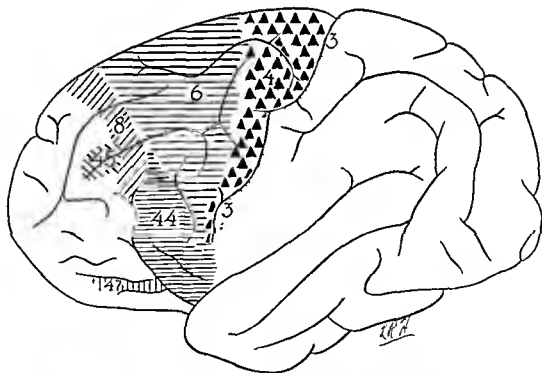
Fig. 17—The precentral motor cortex of the chimpanzee. Compare with figs 4, 6, 8, 9 and frontispiece

Fig. 18.—Area 4 of the chimpanzee. Anterior wall of central sulcus. Note the medium of area 4 (left) into an granular cortex deprived of Betz cells (right). Area 3 is situated to the posterior wall of the central sulcus (not shown). Section prepared in John H. milton for the late Dr. Deser. K. Bateme. Magnification about 65 ×. (Compare with figures 5, 7, 10, 29 and 70.)

FIG. 19.—Area 4s of the chimpanzee. Posterior tip of the superior precentral sulcus (fig. 21 *pres*). Note the presence of large cells in layer *n*. Compare with figs. 11 and 32.

and Fulton (1936). The short description given here is partly based on a study of more than 20 brains in the collection of the Illinois Neuropsychiatric Institute at the University of Illinois. The scheme used by Bailey, Bonin, and McCulloch will be followed fairly closely.

As encephalometric studies show (Cunningham 1892; Connolly 1936; Bonin, 1941), the central sulcus (*ce*) occupies about the same position and runs in the same general direction in the chimpanzee as it does in the macaque (Table 1). The sulcus shows generally two "knees" convex frontad, with an intervening concave bend. It is, as Marchand (1893) remarked, more tortuous than that of the human brain. In its course, particularly at the "knees," it frequently has "spurs" cutting into the adjacent gyri. The upper end of the sulcus may cut into the medial border of the hemisphere. Mingazzini (1928) reports this in three out of thirty

cases (10 ± 5.5%). Retzius (1906). Turner (1866). and Marchand (1893) show the same behavior in some of their specimens. The lower end stops well short of the Sylvian fissure. A deep annectant gyrus between the upper and middle thirds of the central sulcus was described by Cunningham (1892), but neither Mingazzini (1928) nor Walker and Fulton (1936) could repeat this observation.

The superior precentral sulcus (*prcs*) runs roughly parallel to, and about 1 cm. in front of, the central sulcus From about its middle, a spur runs towards the frontal pole. The direction of this spur is taken up by another furrow parallel to the dorsal margin which is known as the superior frontal sulcus (*fs*). It generally ends in a bifurcation The inferior precentral sulcus (*prci*) lies slightly frontad to the superior one and runs also
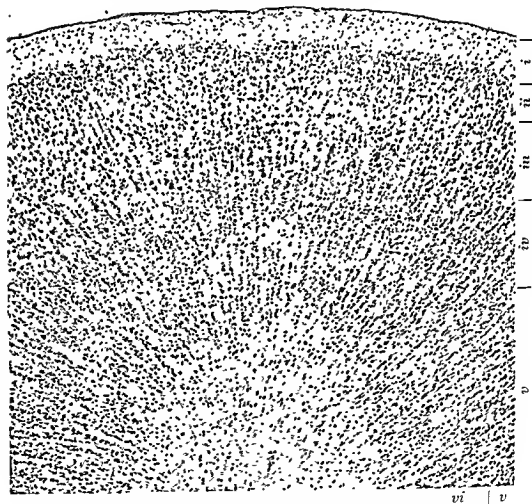
Fig 20 —Area 4t of the chimpanzee Note the faint inner granular layer and the large cells in the lowest part of the third layer Compare with figs 13 and 31

roughly parallel to the fissure of Rolando. In some brains it is broken up into a middle and an inferior precentral sulcus. In other brains it anastomoses with a small spur of the central sulcus. The inferior frontal sulcus (*fi*) takes its origin in the majority of cases from the inferior precentral sulcus.

Some small and shallow grooves are almost always present on the superior frontal gyrus. They are variable and have not been named.

In the ventral or opercular part of the precentral subsector, the fronto-orbital sulcus (*fo*) is the most conspicuous element. It begins on the orbital surface of the hemisphere, and runs for several centimeters onto its lateral side in a frontodorsal direction. In the chimpanzee, it is generally shorter than in the gorilla or the orang. There is much confusion about its nomenclature. According to Marchand (1893), Waldeyer (1891) was the first to employ the name fronto-orbital sulcus in the sense defined here. Walker and Fulton (1936) call it the orbitofrontal.

About 1 cm. further occipitad, a sulcus opercularis (*op*) runs on the frontal operculum. According to Marchand, it is a continuation of the superior limiting sulcus of the insula. Well developed on the ventral side
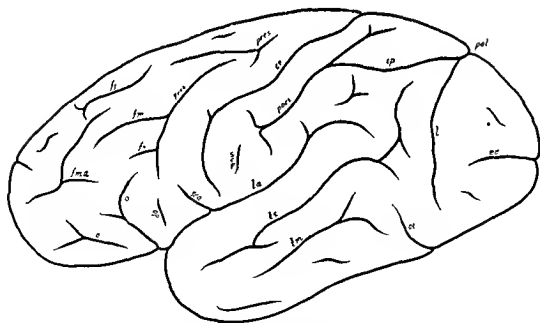
Fig. 21—Fissural pattern of the brain of the chimpanzee, lateral side. Abbreviations: *cc*, centralis (of Rolando); *ce*, *s*, calcarinus externus; *fi*, *s*, frontalis inferior; *fm*, *s*, frontalis medius; *fma*, *s*, frontomarginalis; *fo*, *s*, fronto-orbitalis; *fs*, *s*, frontalis superior; *ip*, *s*, intraparietalis; *l*, *s*, limitus; *la*, lateral fissure (of Sylvius); *o*, *s*, orbitalis; *oi*, *s*, occipitalis inferior; *op*, *s*, opercularis; *poci*, *s*, postcentralis inferior; *pol*, mensura parieto-occipitalis lateralis; *prci*, *s*, praecentralis inferior; *prcs*, *s*, praecentralis superior; *sca*, *s*, subcentralis anterior; *scp*, *s*, subcentralis posterior; *tm*, *s*, temporalis medius; *ts*, *s*, temporalis superior.

of the operculum, it can generally just be seen on the lateral side of the brain where it runs from posteroventral to anterodorsal. Sometimes, however, it joins the fronto-orbital sulcus. It is figured, among others, in Connolly's (1936) figs. 53-55 and in Mingazzini's (1928) fig. 20. Most authors observed it in the majority of the brains they examined, but Walker and Fulton (1936) found it in less than twenty per cent of their cases.

Still somewhat further occipitad, a variable sulcus subcentralis anterior (*sca*) is found. It may or may not cut into the lateral fissure of Sylvius and may or may not be continuous with the inferior precentral sulcus. A large furrow in some brains, it is no more than a small dimple in others. It runs most frequently ventrodorsally.

In the chimpanzee, the posterior boundary of the precentral subsector coincides with the central sulcus almost throughout its length, just as in the macaque (cf. figs. 17 and 21). The ventral continuation of the central fissure marks the boundary between areas 44 and 43. Dorsally, the anterior boundary of the precentral subsector is not reflected by the fissural pattern. There it runs across the superior and middle frontal gyri. Further ventrally, however, it runs roughly parallel to the fronto-orbital sulcus.

Within the precentral subsector, the superior precentral sulcus serves as a fairly reliable landmark for the precentral suppressor area 4s, as the figure of Bailey, Dusser de Barenne, Garol, and McCulloch (1940) shows. The anterior subcentral sulcus indicates the boundary between areas 6 and 44. Again, a leeway of a few millimeters between the sulcus and the architectural boundary has to be allowed.

MAN

General Arrangement

Since our information about the thalamocortical and cortico-cortical connections in the human brain is still fragmentary, we have to base the definition of the human precentral motor cortex mainly on its cytoarchitecture.

Campbell (1905), Brodmann (1909 and 1914), von Economo and Koskinas (1925), and C. and O. Vogt (1926 and 1936) have contributed most to our knowledge (cf. figs. 1-3). Brodmann's latest map, which he published in 1914, differs in a few respects from the one published earlier. It differs also from the map reproduced by Kleist (1934) as Brodmann's. The origin of this latter version could not be ascertained. It appears to be a careless redrawing.

The differences between the various authors will be clear without many

words, Campbell, Brodmann, and von Economo agree fairly well with each other. Many of the discrepancies of Vogt's maps, which unfortunately became widely known when Foerster adopted them, appear to be due to the astonishingly inept handling of the gross features of the brain. Most of their drawings are entirely out of proportion, rendering a faithful representation of finer details utterly hopeless.

In the precentral motor cortex of man (frontispiece) five subdivisions or areas can be recognized. This increase in number over what was found in subhuman primates is due to the fact that the motor area (area 4) can be histologically divided into an "area gigantocellularis" and an "area motorica simplex." We shall refer to the former as 4γ, to the latter as 4a (for agranularis). In front of the latter it appears possible to define histologically the precentral suppressor area 4s. Then follows still further forward the well-known and oft described premotor area 6, and, on the frontal operculum, the precentral dysgranular area 44. These areas differ but little *in their histological appearance* from the homologous areas in other primates. Some of the finer histology to be described in the following pages has been ascertained by studying these lower forms.

The main cyto- and myeloarchitectural characteristics of these areas are the following:

Area 4γ: Agranular, contains giant pyramidal cells of Betz. Unistriate, well-developed radii.

Area 4a: Agranular, no giant cells of Betz, but otherwise the same structure as 4γ.

Area 4s: Agranular presence of large cells in the upper substratum of the fourth layer and no giant cells of Betz in the fifth layer; otherwise a structure similar to that of areas 4 and 6.

Area 6: Agranular, but showing a columnar pattern. Cells are slightly smaller and the second layer is somewhat better demarcated from the third one than in area 4.

Area 44: Dysgranular; small cells intermingled with much larger ones in layer iv. The upper part of layer iv contains numerous very large pyramidal cells (see p. 54). Both layers iii and v can be subdivided. Layers ii and iii are well demarcated against each other. Bistriate, outer stripe of Baillarger lighter than the inner one.

While this scheme does not contain any new facts, it attempts to interpret what is known about man's brain—and to many of its features but scant attention has been paid—*in the light of* what Dusser de Barenne and McCulloch have taught us about the functional organization of the primate brain.
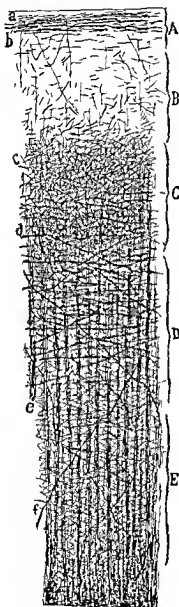
Fig 22.—Myeloarchitecture of area 4γ of man After Cajal (1911 t u figs. 376 and 379)
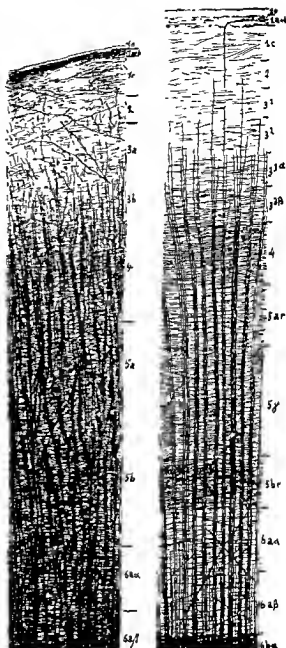
Fig 23.—Myeloarchitecture of area 4γ After C & O Vogt (1919, figs. 30 and 30A) *Left,* ordinary picture, *right,* picture obtained by high differentiation

The fields for the arm, the leg, and the face differ in their areal composition. Area 44 is restricted to the face field. In the arm field, all other areas can be recognized easily. Near the dorsal margin of the hemisphere, i.e., presumably in the leg field (see Chapter XIII), the three subdivisions of area 4 flow together. Betz cells spread out far in front of the central sulcus, so that close to the margin they come to lie even below that strip of large cells in layer *iva* which is characteristic for area 4s (frontispiece). Plate III in von Economo and Koskinas' atlas appears to illustrate this behavior.

Areas 4 and 6

Area 4γ—Area 4γ (frontispiece) was called the precentral or motor area by Campbell (1905), area 4 or gigantopyramidalis by Brodmann (1909), FAγ by von Economo and Koskinas (1925), and *Gig* by C. and O. Vogt (1919, 1936). Within this area the cortex is extremely thick; von Economo and Koskinas measured between 3.7 and 4.5 mm. on the free surface of a gyrus. The boundaries between the various layers, excepting only that between the first and second, are indistinct. For the thickness of the various layers, von Economo and Koskinas gave the figures reproduced in Table II. The average cell size is larger in area 4γ than elsewhere in the cortex, as was shown in detail by Bonin (1938b). The cell density appears to be low in this area, as even a casual inspection of a section will show.

The myeloarchitecture of area 4γ (figs. 22 and 23) was first described by Campbell (1905). After an analysis of the first layer, he proceeded to say that "from the summits of the radiary projection downwards the cortex is so equally and richly stocked with fibers that it is almost impossible to break it up into laminae. . . . At or towards the upper extremity

Table II

THICKNESS OF LAYERS ON THE FREE SURFACE OF GYRI IN MAN
(After von Economo and Koskinas)

Area	I		II		III		IV		V		VIa		VIb
	mm	%	mm	%	mm	%	mm	%	mm	%	mm	%	mm.
4*	0 18	5	0	0	1 47	43	0	0	0 80	23	1 00	29	0 70
6	0 22	6	(0 06)	0	1 30	46	0	0	0 50	20	0 90	28	0 60
44	0 21	8	0 18	7	1 00	37	0 16	6	0 46	17	0 70	25	0 40
5 (upper)	0 26	9	0 12	4	1 00	36	0 20	7	0 46	16	0 70	25	0 45
47	0 30	12	0 08	4	0 99	45	0	0	0 51	23	0 32	15	0 24
24	0 27	11	0	0	0 82	33	0	0	0 80	32	0 57	23	0 37

* Von Economo and Koskinas do not differentiate in their table between area 4s (FA) and area 4γ (F4γ).

of the radiating fasciculi the plexus seems to be especially rich in small fibres." The network diminishes, according to Campbell, in density and possibly in calibre of individual fibers as one goes from the dorsal margin towards the Sylvian fissure.

C. and O. Vogt (1919) classified (from the point of view of myelo-architecture) the area gigantocellularis in the following order: regio unistriata euradiata grossofibrosa, subregio astriata, area typica—which amounts largely to a confirmation of Campbell's results. For the term unistriate means that it is difficult, if not impossible, to discern any lamination. From the description of the Vogts it can, moreover, be accepted that in area 4γ the fine plexus representing the outer stripe of Baillarger is found in the third layer of conventional reckoning and not in the fourth one as elsewhere in the isocortex. Figure 30 of the Vogts was copied by both von Economo and Koskinas (1925) and Rose (1936), but neither of them gave fig. 30A taken from the same area after differentiation had been pushed further in order to illustrate the basic myeloarchitectural pattern (fig. 23).

The laminar pattern (figs. 24 and 29) has been described in much the same terms by most students of cytoarchitecture. It differs, however, from that given by Cajal (1911), which, probably for that very reason, is less known than it deserves to be.

Ramon y Cajal (1911) enumerated six layers: (1) the plexiform, (2) the layer of small pyramidal cells, (3) that of medium-sized pyramids, (4) the layer of large pyramids, (5) the deep layer of medium pyramids and triangular cells, containing the giant cells of Betz and being the homologue of Cajal's sixth layer of the typical cortex, and (6) the layer of fusiform cells, obviously the homologue of Cajal's seventh layer of the typical cortex (cf. Cajal's fig. 333). Elsewhere, as in his fig. 404, he indicates a seventh layer, obviously the zone of transition between the cortex and the white matter. Evidently Cajal was primarily concerned with an analysis of what he actually saw, while the other authors rather strove to pattern their description of area 4 upon the picture found almost everywhere else in the isocortex. The description of area 4γ to be given below (cf. figs. 24 and 29, and also fig. 51) will be based on Cajal's analysis. To avoid confusion, Cajal's layers will be referred to by *small* roman numerals, while the scheme of von Economo and Koskinas will be denoted by *large* roman numerals.

The incoming fibers ascend within the cortex, as Polyak's (1932) March preparations of the macaque well illustrate, in an oblique, often tortuous course. Cajal states categorically, and Lorente de Nó (1943) cites this with the comment that it has to be taken as a statement of fact, that

the afferents form a plexus in the fourth and lower part of the third layer of Cajal's enumeration. But in what Brodmann called the homotypical cortex the level in which the specific afferents break up into a fibrillar plexus is known as the fourth layer.

The first layer of area 4γ contains some horizontal cells of Cajal, and is otherwise filled with an axonal and a protoplasmic plexus. Cajal states that the horizontal cells are more numerous in this area than elsewhere in the cortex. The axonal plexus is fed by the horizontal cells of Cajal, by cells of Martinotti, and by the recurrent collaterals of many pyramidal and fusiform cells situated in the deeper layers of the cortex. The protoplasmic plexus receives abundant supplies from the apical dendrites of the pyramidal and fusiform cells.

In myelin preparations the Vogts (1919) recognized three sublayers (fig. 23). The uppermost of these is almost devoid of fibers, the middle one, fairly thin, contains numerous deeply stained fibers, while the third one, occupying more than half the thickness of the first layer, shows again fewer fibers. Most of them are tangential fibers, but oblique ones can be traced here and there within the third sublayer. Silver preparations after Bodian or Schultze-Stoehr fail to reveal this pattern clearly. However, it
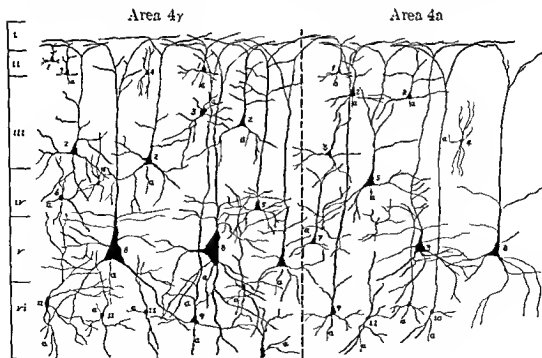
Fig. 24—Some cell types of area 4γ and 4a. Drawn after Golgi preparations. Stratification indicated on left margin; compare with figs. 29, 30, and 51.

is possible to differentiate between a superficial stratum containing almost exclusively tangential fibers, and an inner one, being traversed by some oblique ones.

The second layer contains mostly small pyramidal cells. The basal dendrites of these cells branch out preponderantly in a horizontal direction (fig. 24, 1). The apical dendrite gives off several side branches within the second layer, and sends its end ramifications into the first layer, where they enter the protoplasmic plexus just described. They help to fill the upper as well as the lower substratum, if Cajal's figure can be admitted as proof; the writer has never been able to trace the branches of the apical dendrites in a satisfactory manner. The second layer contains comparatively few fibers; the stripe of Kaes-Bechterew is but poorly developed.

The third layer of Cajal corresponds approximately to layer IIIB of von Economo and Koskinas' (1925, pls. I–IV). It contains medium-sized pyramidal (fig. 24, 2) as well as smaller internuncial cells (fig. 24, 3) with horizontal or ascending axons. The basal dendrites of the pyramidal cells in the third layer are not very numerous and form a comparatively sparse protoplasmic network. They branch out either horizontally or obliquely in a downward direction. The former mode appears to prevail in the upper, the latter in the lower levels of the third layer. The apical dendrite gives off side branches in both the third and the second layer. Double bush cells (fig. 24, 4) are frequently met with in Golgi preparations, but their frequent occurrence may merely be due to the fact that these cells stain more easily than other types.

The fourth layer of Cajal corresponds to IIIC and III(IV) of von Economo and Koskinas. It contains the same type of cells that are found in layer III, but its pyramidal cells are somewhat larger (fig. 24, 5). The basal dendrites of these pyramidal cells are longer than those of the cells in the third layers, and appear to branch more frequently. In short, their "local dendritic field," to use an expression coined by Bok (1936), is better developed. The apical dendrite gives off several branches in the vicinity of the perikaryon. It then rises for a considerable distance through layer iv and the lower part of iii without giving off any further branches. This behavior of the side branches makes it possible to distinguish with Cajal an upper and a lower portion of the apical dendrite.

Apart from pyramidal cells, layer iv contains also a fairly large amount of star cells (fig. 24, 6), the dendrites of which branch within the fourth layer. The behavior of their axons varies. Some of them ascend to more superficial strata, while others descend to deeper ones (see Cajal's fig. 407, D and E). None of them appears to enter the white matter of the hemi-

sphere. They evidently belong to the extensively arborizing type referred to by O'Leary (see Chapter III. p. 101).

Layers *iv* and *iii* contain an axonal plexus made up partly by the specific afferents and partly by the axons and collaterals of cortical cells. This plexus is therefore homologous to what is called the outer stripe of Baillarger in other parts of the cortex, and to what was called the stripe of Gennari by Cajal. Cajal (fig. 25) divided it into three strata: an inferior one, consisting of oblique fibers, a middle one of tangential fibers, and a superior one consisting of end arborizations The inferior stratum, situated in layer *v*, is not a plexus in the sense that it forms a synaptic region It rather consists of "fibres de passage" on their way to the middle and upper strata. The middle stratum in layer *iv* appears to contain synapses, as a study of silver preparations stained after Bodian or Schultze-Stoehr suggests. The upper stratum in layer *iii* is also a synaptic region. If, in the
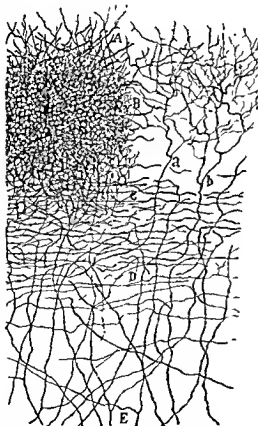
Fig 25—Thalamocortical fibers and their plexuses in the motor cortex After Cajal (1911, t. ii, fig 406).
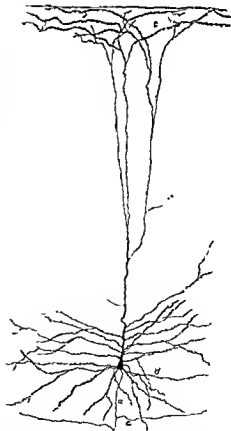
Fig 26—A cell of Betz in Golgi preparations After Cajal (1911, t. ii, fig 369)

homotypical cortex, a layer *w* is defined as that layer which contains the afferent plexus, and if it is further remembered that this plexus frequently sends some of its end arborizations into the lower levels of the third layer, then the difference between the heterotypical motor cortex and the homotypical cortex more or less vanishes. While it remains as true as ever that cytoarchitecturally—one might almost say for outward appearances—the fourth layer is missing, a stratum *m* which the cells are in axosomatic synapse with the fibers of the thalamic radiation is present here just as elsewhere in the cortex. In area 4, however, these "receptive" cells are mostly large pyramidal cells, while elsewhere they are preponderantly star cells or star pyramids. Moreover, in the motor area the outer stripe of Baillarger, or the stripe of Gennari, "spills" over into the third layer to a greater extent than in the homotypical cortex

The fifth layer of Cajal contains again pyramidal as well as internuncial cells. In addition, however, the fifth layer also contains short and medium pyramidal cells (fig. 24, 7) in the sense of Lorente de Nó (1943), i.e., cells which send their apical dendrites not into the first but into the fourth or the lower part of the third layer. It is not possible to divide the fifth layer into the three substrata *va*, *vb*, and *vc* as described by Lorente de Nó for the parietal cortex. The most conspicuous element in this layer in area 4γ are the very cells which have given this area its name—the giant cells of Betz (fig 24, 8). These have been described so frequently that it is almost superfluous to go once more into details. Their shape and the mode of branching of their dendrites have been portrayed by Cajal in his figure 369 (cf. fig. 26). This is said to have been taken from the ascending parietal gyrus where giant cells are present only very close to the dorsal margin of the hemisphere, but it gives nonetheless a good representation of what a giant cell of Betz looks like when impregnated according to Golgi

The basal dendrites of the Betz cells take a slanting course downward, but some of their finer branches may go almost straight down into the sixth layer. Other branches are given off from the sides of the perikaryon. They run generally in a more or less horizontal direction. The apical dendrite gives off several side branches near the cell body. These spread out within layer *v*. Some of them run almost tangentially, while others take an obliquely ascending course. Hardly any, however, seem to present themselves for axodendritic synapses with the axonal plexus in the outer stripe of Baillarger by extending as far as layer *iv*. The apical dendrite runs clear through layers *iv* and *iii*, giving off scarcely any side branches (now and then a thin branch can be observed). It breaks up into a fork within layer *ii* or *iii*, and sends its final ramifications into the first layer, just like any other pyramidal cell. The cells of Betz, in common with other

"efferent" cells in layer *vb*, have **no axosomatic** and a minimum of axo-dendritic synapses with the **outer stripe** of Baillarger. Incoming impulses can affect them therefore only indirectly. The axons of the Betz cells arise from the base of the perikaryon, where Nissl preparations frequently show an axon hillock. The axon is directed toward the white matter and enters the internal capsule forming a constituent of the pyramidal tract (see Chapters V and VI), or of the **cortico-bulbar tract**, depending upon the location of the Betz cell. Within the cortex it may give off horizontal or ascending (recurrent) collaterals as described by Cajal (1911). Cajal states that the spider cells and the double bush cells in layer *v* are identical with those found in the higher levels of the cortex for which he had described them in great detail. This would mean that the Betz cells are surrounded by pericellular "nests" made up by the axons and the telodendria of these small cells. It is clear from Cajal's drawings (figs. 27 and 28) that the synaptic fields on the perikarya of the Betz cells are heterogeneous in the sense of Lorente de Nó (1938) (see particularly the regions near *b* in both fig. 27 and fig. 28). As will be remembered, Lorente de Nó demonstrated that, within a given region of the surface of a cell body, all synapses come in some cases from one axon while, on other cells, the synapses are formed by several axons. The former homogeneous synaptic fields are trans-mitting impulses from a single cell, the latter heterogeneous synaptic fields are totally activated only when impulses from all "participating" cells arrive within about a millisecond's duration.

The cells of Betz are largest in the dorsal part of area 4γ, and gradually decrease in size ventrally. They are found either singly or in small groups of three or four cells. According to Brodmann (1909), the solitary ar-rangement prevails in the ventral part of the area, while a "cumulary" arrangement is found in its dorsal part. For the execution of individualized movements, as of hands and face, the former may be better adapted than the latter. Before a formal theory can be elaborated, however, we require more detailed and precise information about the origin and ending of the pyramidal fibers than we have at present.

The total number of the giant cells in the human brain was given by Campbell (1905) as 25,000. Lassek (1940) found 34,183 on the right, and 34,562 on the left side of the brain of a 22-year-old negro woman. The two sides differ by less than 2%, and a mean of 34,370 can certainly be ac-cepted as reliable. Neither of these **authors** appears to have included the giant cells in the postcentral sector.

The size of the giant cells has been measured by Bonin (1938b) and by Lassek (1940). The former measured only the cells in the dorsal part of the precentral gyrus, at the level of the first frontal convolution, while

the latter measured cells throughout area 4γ. Moreover, Bonin measured the volume of the nuclei, while Lassek measured the surface covered by the silhouette of the cell bodies. The distribution curves of Lassek are definitely skew, with the "tail" towards the larger volumes, while the curve obtained by Bonin is essentially symmetrical. Moreover, if the figures given by the two authors are used to compute the surfaces of the cell bodies the results will be found to differ by more than 50%. Bonin's results
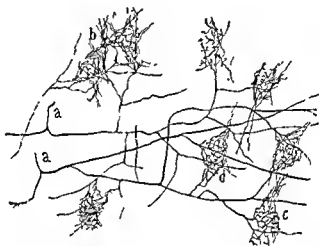
Fig 27—Pericellular nests formed by axons of internuncial cells around the perikarya of pyramidal cells After Cajal (1911, t ii, fig 361)

Fig 28—Pericellular nests around perikarya of pyramidal cells After Cajal (1911, t ii, fig 362)

show a mean nuclear volume of $2328\mu^3$, leading to a mean surface of the perikarya* of $8900\mu^2$; Lassek computed the mean area of outline as $1757\mu^2$, leading to a mean surface of the perikarya* of $6300\mu^2$ for the leg field and $5600\mu^2$ for the whole of area 4. It is permissible, in any event, to assume that there are at least 1000 "axosomatic" synapses on a Betz cell.

The sixth layer presents few characteristic features. It contains pyramidal (fig. 24, 9) as well as fusiform cells (fig. 24, 10). Both types can be further subdivided according to the behavior of their apical dendrites, which may be long, reaching the first layer, or medium, reaching only the third layer, or short (fig. 24, 11), reaching no higher than into the fourth layer. Another noteworthy feature is the blurred boundary against the white matter of the hemisphere. There is a broad zone of transition which, as we saw, was labelled layer *vii* by Cajal.

Ontogenetic data have been supplied by Brodmann (1905), Aldama (1930), and Conel (1939, 1941). Brodmann (1905) showed in Nissl preparations that during fetal life his area 4 exhibited a well-developed inner granular layer. That this layer is still present at birth is shown in Conel's (1939) photographs of Nissl and Golgi preparations. Of the "leg" field Conel says that the fourth layer "is not distinct," of the paracentral lobule that "the layer can be easily identified," of the arm region that it is "definitely outlined," and of the face region that it is "not very distinct." In the month-old child studied by Conel (1941) the inner granular layer is less clearly defined than in the newborn, but can still be discerned. Aldama (1930) using Nissl preparations saw remnants of that layer in a child of eleven months. He adds that this layer is more pronounced in the anterior wall of the sulcus of Rolando than further forward. Aldama found traces of the inner granular layer still in the brain of a five-year-old child. According to Conel, the giant cells of Betz are the most advanced cells of the new-born if the degree of development of their processes is taken as a criterion.

Brodmann's contention that the "heterotypical" cortex of area 4γ developed out of a homotypical cortex is true enough from a restricted cytoarchitectural point of view. We lack, however, complete information, which can only be furnished by silver preparations.

The outstanding characteristics of area 4γ, which it shares with areas 4a, 4s, and 6, are: (1) absence of an inner granular layer in the cytoarchitectural sense, (2) low cell density, but large average cell size, (3) preponderance of pyramidal cells, and (4) a confluence of the outer and inner

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* Based on Bok's (1936) formula, and on the assumption that the cell body is a cone and $h = 6r$ (h = height; r = radius of base)

stripes of Baillarger. These characters have gradually evolved during phylogenesis, and it is tempting, therefore, to correlate the trend of architectural evolution with a trend in functional evolution, if such a trend can be discerned. In almost every textbook can be found the statement—and everybody who has had any experience in the laboratory will confirm it—that the movements which can be elicited from the motor cortex become more "individualized," broken up into "fragmentary local items of movement" to quote Walshe (1947), the higher in the phylogenetic scale the animal stands. The detailed evidence may be found in Huber's (1934) memoir.

On the structural side, the relation of the pyramidal cells and their dendrites to the various layers, and the structure of the axonal plexuses remain apparently unchanged among the primates. Two other trends, however, can be discerned (see pp. 64 *et seq.*). The relative size of the Betz cells increases, and the cell density decreases.

The former trend may affect the nature of synaptic transmission, the latter may affect the electrical influences to which Adrian (1947) called attention.

Pyramidal cells (perikaryon plus dendrites) are in synaptic connections with axons in many layers. Excepting the medium and short pyramidal cells all true pyramidal cells are influenced by events in the tangential layer as well as in layers *ii* and *iiia*. for even many of the small cells in layer *ii* send their basal dendrites into layer *iiia*. Those in layers *iiib* and *iv* are still influenced by the first layer, and in addition are under the direct influence of events in the outer stripe of Baillarger. The pyramidal cells in the fifth layer, while avoiding, as it were, the outer stripe of Baillarger, are through their apical dendrites in connection with the "supragranular" layers, and through their basal dendrites in contact with the inner stripe of Baillarger.

The divisibility of pyramidal cells into topographic zones, each of which receives a specific kind of afferent impulse, was stressed by Lorente de Nó (1934) in his study of the ammonic system. It is perfectly obvious, and indeed was pointed out by Lorente de Nó himself, that this also holds true for the cortical pyramidal cells. A preponderance of pyramidal cells as in 4γ means that most of the cells are in synaptic connections with several of the axonal plexuses.

The relation of the apical dendrite of the large and giant pyramidal cells in layer *v* to the outer stripe of Baillarger makes it at least very probable that the axodendritic synapses within that stripe alone are insufficient to "fire" these cells. Since these cells are the source of the efferent fibers

from area 4γ, it follows that an efferent impulse must be due to the activity of many internuncial neurons and that afferent "sensory" impulses delivered to area 4γ from the thalamus can do no more than provide a "background activity." One aspect of the manner in which the cerebellum and the basal ganglia can control motor performances may be deduced from these considerations (cf. Chapter X).

The confluence of the two stripes of Baillarger is not due to a downward extension of the outer stripe but rather to a diffuse spreading of the inner one. The outer stripe is similarly diffuse on its outer side. Obviously, the broader the stripe the more cells will be under its sway. But within area 4γ relatively many of these cells are pyramidal with heterogeneous synaptic fields. It follows (cf. figs 27 and 28), that impulses coming through a stripe of Baillarger are by themselves incapable of firing a pyramidal cell. They have to be "supported" by the other constituents of the synaptic field. The broad and somewhat diffuse arrangement of the stripes of Baillarger in 4γ increases the probability of causing cortical cells to discharge upon receipt of an afferent stimulus. In a way, but not in every respect, this arrangement compensates for the large cell size and the preponderance of pyramidal cells.

The larger relative size of the Betz cells can reasonably be assumed to mean a more complicated organization of the synaptic fields on their cell body, thereby requiring messages from a greater number of cells to arrive "nearly simultaneously" in order to fire a given pyramidal cell The reduced cell density would lead to a greater average distance of cell bodies as well as of apical dendrites thereby reducing the electrical influence of cells upon each other. Both factors thus can be interpreted as favoring a greater differentiation of patterns of activity in higher forms, especially, of course, in man.

"Patterns of activity" denote physiological processes, not the effects of electrical stimulation. If nothing else, then Rasmussen and Penfield's (1947) observation that electrical stimulation of certain parts of the face field will impede articulate speaking should demonstrate the havoc wrought by the application of a pair of electrodes to the cortex.

Area 4a—The area 4a covers most of the free surface of the precentral gyrus at the level of the middle and inferior frontal gyrus and extends further ventrad than the area gigantocellularis. Brodmann (1909), as well as C. and O. Vogt (1919), considered it as a part of area 6 (see above, pp 5

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[2] The experiments by Marshall, Woolsey, and Bard (1941) and by Adrian (1941) show that the afferent impulses to the precentral cortex can not be "sensory" in the ordinary sense of that term This does not contradict Dusser de Barenne's famous strychnine experiments
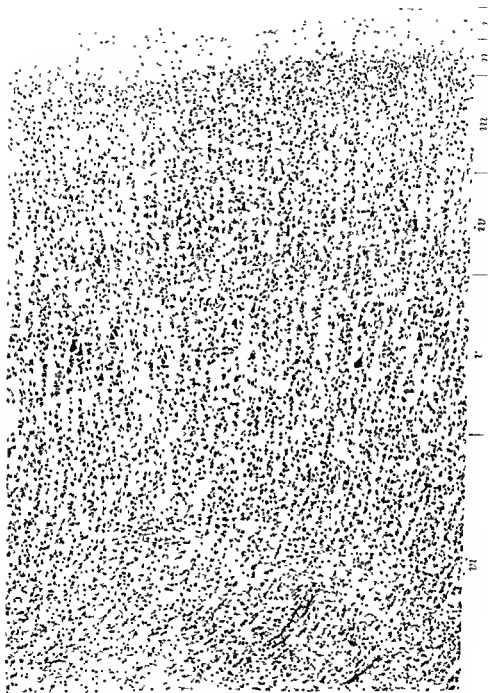
FIG. 29 — Area 4γ of the human brain. **Toluidin blue.** After von Economo and Koskinas (1925 plate II). Magnification about 45:1. The layers described in the text are indicated on the right margin. Compare with fig. 24 and with figs. 5, 7, 10, and 18
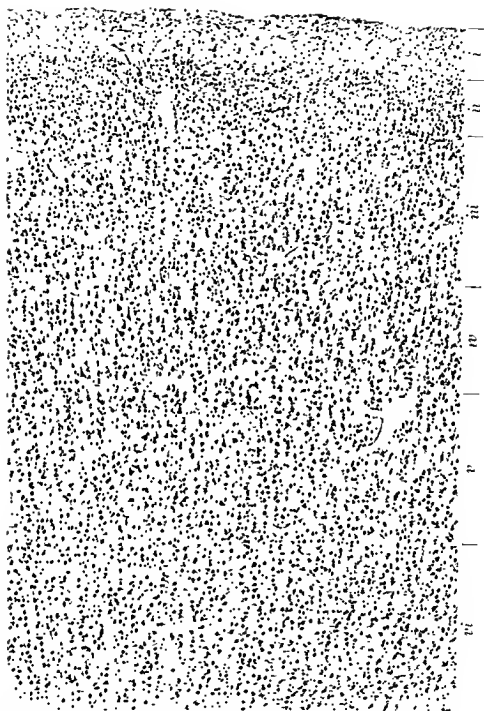
Fig 30—Area 4a of the human brain Toluidin blue After von Economo and Koskinas (1925, plate V). Magnification about 45 1
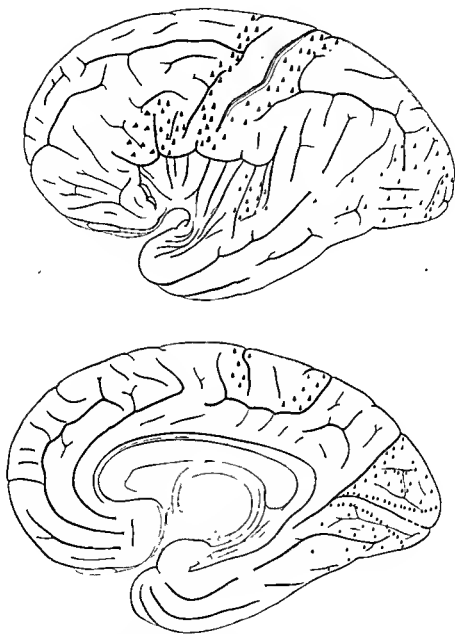
Fig 31—Distribution of large cells in layer iii a After von Economo and Koskinas (1925, figs 74 and 75) Note the strip along the superior and inferior precentral sulci, corresponding to area 4s Compare with frontispiece
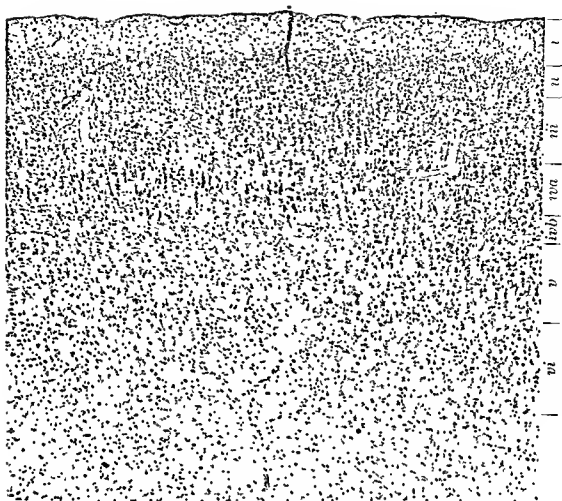
Fig. 32.—Area 4s of the human brain. Cresyl violet. Own preparation. Magnification about 45 : 1. Compare with figs. 30, 11, and 19.

and 18). The first to recognize it histologically were von Economo and Koskinas (1925), who called it FA. The area so designated by them may have included, however, the precentral suppressor area. The architecture of area 4a (fig. 30) appears to be identical with that of area 4γ, excepting, of course, the absence of Betz cells in 4a. It should also be noted that area 4a differs but little, microscopically, from area 6, thus accounting for the conclusion reached by Brodmann (1909) and others. Furthermore, were it not for the fact that area 4s separates it from area 6, we, too, would place it with area 6 rather than area 4. It may be regarded as homologous to area 4r in the chimpanzee (see pp. 214 and 215), but its physiological characteristics have not been determined in sufficient detail to demonstrate its precise role in the execution of movements.
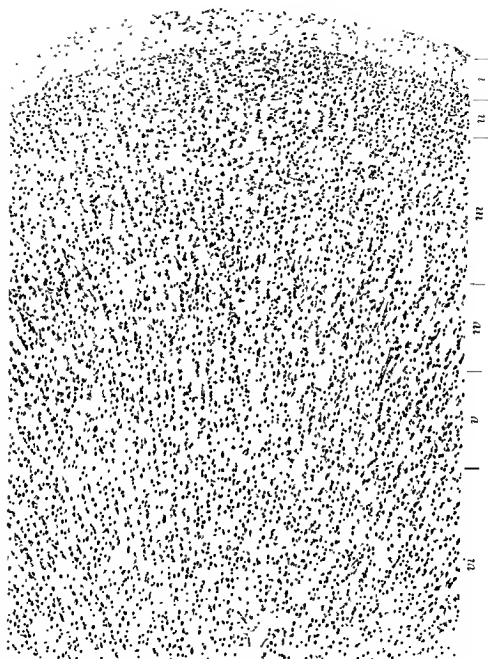
FIG. 33—Area 6 of the human brain. Toluidin blue. After von Economo and Koskinas (1925 plate VI). Magnification about 45:1

Area 4s—A band of particularly large cells in layer *iva* was found by von Economo and Koskinas all along the precentral sulci (see fig. 31) and was considered by them as a part of their area FB. They mention, however, that these large cells are present only in the posterior part of FB. This formation may be seen on their plates V and IX, and is shown in fig. 32 here. Except for these cells in layer *iva*, its architecture differs very little from that of areas 4a or 6, as Hines (1937) was the first to point out. In the light of our present knowledge, it appears reasonable to look upon the strip containing this band of cells as 4s (see footnote 50, p. 80).

Area 6—Area 6 lies immediately in front of the precentral suppressor area (area 4s). It makes up the largest part of what Brodmann called area 6. It is practically identical with von Economo's area FB or with area 6aβ of Vogt. It differs from areas 4y and 4a by the fact that the cells of layers *iii* and *v* are arranged in columns and that by and large the cells are smaller than in area 4 (fig. 33). The cortex as a whole is slightly thinner, and its stratification is a trifle more pronounced. Area 6 receives, as was shown by Polyak (1932) for the macaque, only scant specific afferents. The scarcity of these oblique fibers may very well be the reason for the columnar pattern of this area. Since the stratification of 6 is very similar to that of 4, it appears unnecessary to go into details.

The Dysgranular Area 44

The face field contains in addition to the areas mentioned thus far, the precentral dysgranular area 44 (fig 34) It was designated by Brodmann (1909) as 44 and on a later map (1914; cf fig. 2A) as 44 in its posterior and 44a in its anterior part Von Economo and Koskinas called it FCBm and referred to it as Broca's area It was investigated by Knauer (1909), Riegele (1931), Kreht (1936b c) and Strasburger (1938), all of whom worked under Vogt, as well as by Stengel (1930) who worked under von Economo Vogt's co-workers subdivided area 44 into two areas which they called 56 and 57, and which appear to coincide roughly with 44 and 44a of Brodmann's last map Similarly, Stengel states that the anterior part of the pars opercularis of the third frontal convolution is covered by a cortex somewhat more granular and containing smaller pyramidal cells than that covering the posterior part He found these structural differences in three brains examined by him, but failed to find them in two others. Foerster (1936b) observed the phenomenon of "denervation" upon stimulating the anterior part of Broca's area. But he added, "It is difficult to say whether *post hoc ergo propter hoc.*" A similar observation was recently reported by Meyers (1941). The phenomenon of "denervation" was, so far as the
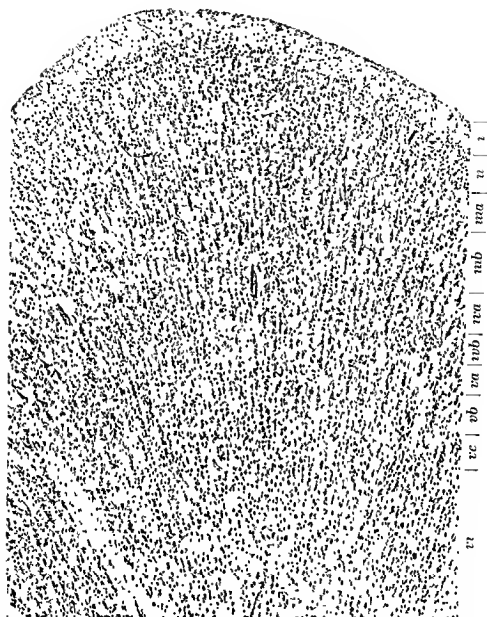
Fig. 34.—Area 44 of the human brain. Toluidin blue. After von Economo and Koskinas (1925, plate XIV). Magnification about 45:1. Note the large cells in *tca* and *tb*. Compare with figs. 20, 13 and 35.

writer is aware first described by C. and O. Vogt (1919). They appear to have stimulated what Dusser de Barenne and McCulloch (1938a) called a "suppressor area." Observations upon the macaque and chimpanzee (see Chapter VIII) make it probable that area 44a belongs to the frontal

suppressor area. We shall, therefore, put the anterior limit of our precentral dysgranular area near Eberstaller's sulcus diagonalis, keeping in mind, however, that there is no very close correlation between the border of the dysgranular precentral area and that variable furrow. To call area 44 Broca's area is unwarranted. "Broca's circumvolution" originally was understood to be the third frontal convolution (see Dejerine, 1895, I, p 255) in its entirety. Broca's area is now understood to be the motor speech center—a highly problematical conception with which Anatomy should not be burdened.

The architecture of area 44 (figs 34 and 35) differs in many respects from that of the rest of the precentral subsector. It shows a well discernible internal granular layer, and the third and fifth layers, too, show definite substrata, not recognizable in the areas described thus far. It is in keeping with this tendency towards a more "elaborate" lamination that the myeloarchitecture, too, shows a definite stratification with a separation of the two stripes of Baillarger.

AREA 44
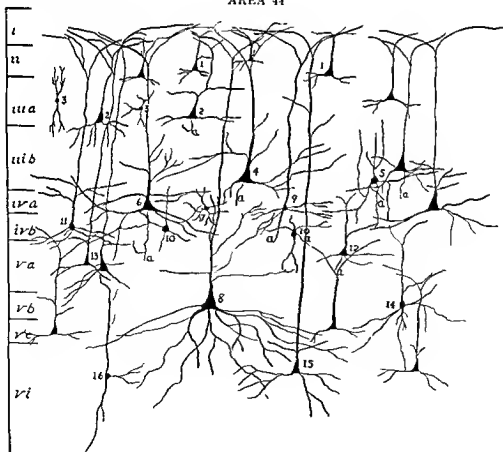
Fig 35—Some cell types of area 44 in Golgi preparations.

The molecular layer is trizonal in myelin preparations. Strasburger (1937) describes layer $ia + b$ as poorer in fibers than the neighboring areas

The second layer is described by Kreht (1936b) as narrow, with somewhat larger cells exhibiting a greater variation in their size than in area 57 which is frontal to 56. The cells of layer ii are smaller, however, than in area 4γ. Pyramidal cells (fig. 35, 1) appear to prevail, as Conel (1941) also has shown. There is no well-developed stripe of Kaes-Bechterew in area 44.

The third layer has been divided into three sublayers by von Economo and Koskinas, Riegele, and Kreht. According to these authors, layer IIIa is narrow, Layer IIIb is much broader and is more sparsely populated by small cells. Layer IIIc, slightly narrower than IIIb, is characterized by lesser cell density and by much larger cells. Von Economo and Koskinas emphasize the presence of very large or "giant" cells in the lower part of IIIc which form a distinct sublayer.

For reasons which, it is hoped, will become clear as this analysis progresses, it appears more reasonable to put the lower border of the third layer a little higher, namely, above the layer of the "giant cells," and to subdivide the third layer into two substrata. The upper one of these, layer *iiia*, corresponds roughly to IIIa of von Economo and Koskinas, and to III[1] of Kreht and Riegele Golgi preparations reveal no startling features in this substratum Pyramidal (fig 35, 2) and internuncial cells (fig. 35, 3) look very much the same as anywhere else in the cortex. The division between layers ii and *iiia* is based mainly on the difference in cell density

In layer *iiib* the types of cells (fig. 35, 4 and 5) are again the same as in other cortical areas, so that a detailed description would be but a wearisome repetition The basal dendrites of many, if not of all, pyramidal cells in layer *iiib* (fig 35, 4) send branches into the outer stripe of Baillarger They may thus have axodendritic synapses with the specific afferents, while the cells in layer *iiia* can receive impulses from the specific afferents only through internuncial neurons.

Having redrawn the boundary between the third and the fourth layer, it now becomes possible to subdivide the fourth layer into two substrata. The upper one, *iva*, corresponds, as we saw a moment ago, to the lower part of IIIc of the conventional stratification. It is characterized by the "giant cells" described by von Economo and Koskinas. Since the term "giant cells" may give rise to confusion with the cells of Betz, we shall call these cells henceforth "huge cells" or "huge" pyramidal cells (fig. 35, 6) These pyramidal cells show a dense and well-developed system of basal dendrites which tend to ramify in a horizontal direction. The local dendritic field is consequently almost completely restricted to the fourth

layer. The apical dendrite gives off several side branches near the cell body. The lower ones of these take their course in the upper levels of layer *iv*, those that come off a little higher take their course within layer *iub*. The upper portion of the apical dendrite ascends then through the rest of the third and through the second layer, to split up into its end ramifications in the molecular layer. No side branches could be observed on that portion, although frequently the stem of the dendrite breaks up into its two main branches within the second layer. In addition to the huge pyramidal cells, layer *iva* contains small interunial cells (fig. 35, 7) and occasional star pyramidal cells (fig. 35, 9).

Layer *ivb* contains small star cells (fig. 35, 10) as well as other cells of Golgi's type II. Fairly large pyramidal cells (fig. 35, 11) are also found here and there. It is the presence of these large cells in *ivb* that gives Broca's area its characteristic dysgranular appearance.

The whole breadth of this redefined fourth layer contains the outer stripe of Baillarger. It is because of this relationship that the conventional layer IIIc is here referred to as layer *iva* The writer was able to study this plexus in preparations stained after Weigert-Kultschitzky and Bodian, but did not succeed in impregnating it after the method of Golgi. Hence no details can be added to the bare statement of its presence. The most important question concerning this plexus is, of course, that of its composition. It is known that it contains in most cortical areas both intracortical association fibers and specific afferents from the thalamus. That the former class is by no means a negligible component, even in cortical areas receiving an abundant supply of specific afferents, was only recently demonstrated by Le Gros Clark and Sunderland (1939) in the case of the striate area The presence of intracortical association fibers within area 44 will readily be granted Are there also specific afferents? A careful survey of the lower strata of area 44 revealed fairly numerous oblique fibers both of thin and thick calibre. While some of them are without doubt ascending axons of cells of Martinotti, others can justifiably be claimed to be specific afferents entering presumably the outer stripe of Baillarger. It should be added that Aramovich (1939) in his myelogenetic studies on Broca's area fails to indicate these oblique fibers

The fifth layer has been divided by most writers into two sublayers. Large pyramidal cells are sometimes found so close to the fourth layer as to be almost within that layer. They form frequently veritable nests, as can be seen on von Economo and Koskinas' photographs (compare fig. 34). However, a consistent layer of large pyramidal cells can be made out a short distance below the fourth layer. It is thus possible to subdivide the

conventional layer Va once more into two sublayers which clearly correspond to Lorente de Nó's (1943) sublayers *va* and *vb*. Layer *va* would then be described as containing generally smaller cells, among which short and medium pyramidal cells (fig. 35, 12) occur, and as showing here and there nests of larger pyramidal cells (fig. 35, 13). The writer was not able to identify these cells in Golgi preparations, so that he is unable to describe their shape in detail. In layer *vb* are found, according to Lorente de Nó, the pyramidal cells giving rise to efferent projection fibers. In area 44 these cells (fig. 35, 8) are generally well below the size of the corresponding cells of Betz in area 4γ, yet occasionally they may attain the size of giant cells. It so happened that the largest cell the writer ever encountered in his measurements was situated in Broca's area. In Golgi preparations, the efferent pyramidal cells can readily be identified. Their basal dendrites run for long distances in the fifth and sixth layer. While some of these branches take an oblique course, others dip almost radially into the sixth layer (This is accentuated in fig. 35, 8, since some of the dendrites, arising near the middle of the base, are seen in perspective foreshortening.) The apical dendrite gives off a number of branches in its lower portion. Some of these side branches take an oblique ascending course and appear to run partly in the fourth layer. It is hard to be quite sure about the boundaries of the cortical layers when studying Golgi preparations, since generally only a few cells are impregnated. Yet repeatedly the writer was able to follow these dendritic branches into layer *iv*. The presence of axodendritic synapses between the outer stripe of Baillarger and the efferent pyramidal cells has to be reckoned with in area 44, just as, e.g., in the parastriate area where similar cells were observed by Bonin (1942) and O'Leary (see Chapter III). O'Leary describes these dendrites as going even beyond the fourth layer. The upper portion of the apical dendrite is almost devoid of side branches. It breaks up into its end ramification in the molecular layer.

Layer *vc* (von Economo and Koskinas' layer Vb) is sparsely populated by smaller cells, mostly medium and short pyramidal cells (fig. 35, 14) in the sense of Lorente de Nó (1938a). In addition, *vc* contains the axonal plexus of the inner stripe of Baillarger. According to Strasburger (1938), the inner and outer stripe appear almost equally dense in myelin preparations, although the inner one is sometimes slightly denser.

The sixth layer contains pyramidal (fig. 35, 15) and fusiform cells (fig. 35, 16). It can be subdivided into two substrata as in most other cortical areas. It does not show any features specific for area 44, and we dispense therefore with a detailed description. Suffice it to add that the border between the gray and the white matter is indistinct, although sharper than in area 4γ.

The histological differences between the dysgranular area 44 and the agranular portion of the precentral motor cortex may be assumed to express functional differences between these two parts.

Due largely to the fact that the outer stripe of Baillarger is shifted further towards the surface in the dysgranular cortex than in the dysgranular cortex, the "supragranular" layer, and with it the internuncial apparatus lodged here is better developed in the latter. Moreover, this apparatus is composed of cells which are smaller and more densely packed than in the agranular cortex. From the work of Lorente de Nó and from all the experiences of modern neurophysiology (see Chapter III), it is clear that all cortical events must be thought of as drawing a large number of cells into their activity and as establishing within a given space something that can be likened to, and understood as, a physical field, using the term field in the sense in which it is used in such concepts as gravitational, or magnetic, or electrical field. Köhler (1938) and more recently Köhler and Wallach (1944) discussed these conceptions as the theory of isomorphism.

Spread of excitation within the cortex is still little understood. Synaptic transmission and electrical influences of neighboring neurons (see p 44) are the two mechanisms known at present which are responsible for that spread. To consider the cortex as a homogeneous medium is permissible only as a first approximation, and tends to overemphasize the effects of electrotonus. The perfectly homogeneous substrate of a field would be afforded by a cortex in which the cell size is so small as to be infinitesimal relative to the extent of the field. Even the various types of komocortex, including the striate area, are far from this ideal. If, however, the cells are exceptionally large and scarce, as in the motor cortex, their electrical influence upon each other will be negligible, and heterogeneous synaptic fields will be present almost everywhere [*] Both factors will tend to diminish the field character of cortical processes. This is particularly true for areas 4 and 6, while the structure of area 44 suggests the possibility of cortical "fields."

In any case, the appropriate treatment of events in the precentral motor cortex is along the theoretical lines laid down by McCulloch and Pitts (1943) or Shimbel and Rapoport (1948).

It should be emphasized, moreover, that the concept of cortical fields (in the dynamical sense of this term) plays a different role in a theory of the motor cortex from that which it plays in a theory of the sensory cortex.

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[*] The probability for a small cell with a homogeneous synaptic field to be caused to fire is obviously greater than that for a large cell with heterogeneous synaptic fields. It is possible, on the other hand, that the larger "local dendritic field" of a large cell makes up for the lesser cell density as far as electrical effects are concerned

In the latter case, the field is subsequent to events in afferent fibers, and it has been possible, as Marshall and Talbot (1942) have shown, to arrive at a satisfactory theory by restricting discussion to stationary fields, i.e., by neglecting the dimension of time. In the motor cortex, on the other hand, this field, if it plays any role at all, must be considered to precede events in efferent fibers, and it appears impossible to arrive at a satisfactory theory of cortical activity while neglecting the dimension of time. The relations of dynamical fields to incoming and to outgoing events is forcefully brought out when written down in the notations developed by McCulloch and Pitts (1943). Also, activity of the motor cortex is instigated by cortico-cortical afferents (see Chapter VIII) (and intracortical processes?) converging upon area 4 from area 6, from the parietal region (body scheme!) as well as from the infraparietal plane (second motor area, see p 9) But these cortico-cortical afferents end in the inner stripe of Baillarger and in the stripe of Kaes-Bechterew.

Large size and low density of cells may favor the establishment of comparatively large reverberating circuits or "feedback" systems. The discussion by Rosenblueth, Wiener, and Bigelow (1943) of purpose and of negative feedback may well prove to be of great interest for a theory of the motor cortex.

Within the outer stripe of Baillarger the incoming impulses impinge in area 44 among others upon the huge cells of layer *iva* (fig. 35, 6). The synaptic fields on these huge cells are almost certainly heterogeneous. Pericellular nests within layer *iva*, evidently around the huge pyramids were seen by the writer in Golgi preparations, but it was not possible to determine the exact origin of the axons entering these nests. It is nonetheless reasonable to assume that some of the axons come from the plexus of the outer stripe of Baillarger and convey impulses from the specific afferents. These specific afferents, however, can cause these huge cells to discharge only when there is a sufficient "background" activity so that all synapses of a given synaptic field are activated within about a millisecond. But "background" activity presupposes the existence of a cortical field, while the specific afferents *can*, at any rate, function in such a way as to deliver a spatially very restricted impulse. It may be useless to pursue this line of thought much further, yet enough has probably been said to realize that histological considerations not only lead to the problem of "field" versus "mosaic" but in some way may even help to reconcile the two views.

The "efferent" pyramidal cells of area 44 (fig. 35, 8) have a relatively large number of axodendritic synapses with the outer stripe of Baillarger. We do not know whether these axodendritic synapses raise or lower the

threshold of the "efferent" pyramids. At any rate, the fact that the efferent pyramidal cells in area 44 differ in their synaptic relations from those found in 4γ deserves attention.

Gross Anatomy

The fissural pattern of the human brain has been studied for almost a century with great assiduity without, however, proving much more than its great variability. The older literature has been reviewed and listed by Genna (1924). Since then Shellshear (1937), Chi and Chang (1941), Connolly (1941), and many others have contributed further material.

The central sulcus has about the same position in the human brain that it has in that of the other primates (see Table I, p. 23). In the majority of cases the sulcus cuts into the upper margin of the hemisphere. Cunningham (1892) examined 52 hemispheres and found: $60 \pm 6.8\%$ cutting into the upper border, $21 \pm 5.6\%$ just reaching it, and $19 \pm 5.4\%$ falling short of it. (The standard errors have been added.) In that same material Cunningham found that the sulcus reached the Sylvian fissure in $19 \pm 5.4\%$ of all cases. He mentions that Benedict found this condition in $47.5 \pm 8.1\%$ of his 38 cases, while Giacomini reported it in only $6.2 \pm 1.5\%$ of his 336 hemispheres. While the difference between Cunningham and Giacomini may have arisen by chance in about 2% of all cases, the other differences are clearly significant. Whether they are actually racial differences or whether they express merely the "personal equations" of the different observers must be left undecided.

On the basis of a detailed study of the conformation of this sulcus, Symington and Crymble (1913) rejected the hitherto adopted method of analysis by "knees" or "bends" and pointed to the constant occurrence of two "buttresses" in the anterior wall of the sulcus. These buttresses may cause more or less pronounced bends in the fissure. An additional upper or lower buttress may be present and cause further bends. In 237 hemispheres of adults two buttresses causing (indirectly) two bends with convexity frontad, were present in 131 cases ($55 \pm 3.3\%$). At the level of the upper buttress, a submerged gyrus is always present. Symington and Crymble measured the length of the Rolandic fissure by determining the distance between the upper and lower end-points both along a straight line and along the tortuosities of the sulcus. Their data are given in somewhat summary form. The results that could be distilled out of them are: straight length of sulcus of Rolando. 91 ± 0.6 mm.; length of sulcus measured along its bends, 102 ± 0.7 mm. The anthropologically minded could, in an obvious manner, compute an index of tortuosity of 112, but in the absence of comparative data this is not particularly enlightening.

Ontogenetically the sulcus arises, as Genna and others have pointed out, from two anlagen. These unite at the level of the superior buttress Cunningham pointed out that the submerged gyrus just mentioned was situated at this level and went on to discuss cases of a bipartite sulcus such as have since been described by several other authors (e.g., by Chi and Chang). This mode of development is usually interpreted as proof for the conception that the central sulcus has arisen by the confluence of the coronalis and the ansata of lower mammals (cf Ariens Kappers, Huber, and Crosby, 1936).

Roughly parallel to the central sulcus are the superior and the inferior precentral sulci. They may be united, but that appears to be the exception rather than the rule. Thus Chi and Chang found that the two sulci were united in only $17 \pm 3.5\%$ and were separate in $83 \pm 3.5\%$ of the Chinese brains they examined.

It is only in man that the Sylvian fissure sends off anterior rami which cut into the frontal operculum. There may be only one ramus present. there may be the classical picture of an ascending and a horizontal ramus separate from each other, the two may form a Y, or there may even be three rami Chi and Chang found one branch in $12 \pm 3\%$, two branches in $85 \pm 3.5\%$, and three branches in $3 \pm 1.6\%$. Connolly (1941) found one branch much more frequently on the right than on the left side. The frequencies were:

	Whites	Negroes
Right hemisphere	$23 \pm 7.7\%$	$26.7 \pm 8.0\%$
Left hemisphere	$0.7 \pm 1.5\%$	00

There is a significant difference between the right and the left side but none between the brains of whites from Berlin in Germany and of "full-blooded" American Negroes. Even the differences between Chi and Chang's and Connolly's material are not statistically significant. Thus two branches may be considered as the usual configuration.

For our present purpose, only the ascending ramus is of importance, since it marks, in a vague sort of way (*v. infra*), the anterior limit of the precentral motor cortex. The cortex bordered below by the main stem, and in front by the ascending ramus of the Sylvian fissure is the opercular part of the third frontal convolution. The much-discussed question of a partially exposed insula has no direct bearing on our problems.

The sulcus subcentralis anterior is generally no more than a small indentation arising from the posterior branch of the Sylvian fissure and cutting into the frontal operculum. It varies considerably in size. Sometimes it is superficially united with the lower end of the central, or, more rarely, with that of the precentral sulcus. The former case has been discussed in detail by Eberstaller and by Symington and Crymble.

The sulcus diagonalis of Eberstaller (1890) was described by the author in these words: "On the pars opercularis of the third frontal convolution there is generally a sulcus which extends obliquely from behind and above to in front and below and is of rather variable depth and degree of development. This is the diagonal sulcus." It may be (A) connected with the precentral sulcus, or it may be (B) all by itself, or it may be (C) connected with the inferior frontal sulcus. In the brains depicted in Retzius' (1896) atlas the frequencies were: A, $45 \pm 9\%$; B, $32 \pm 8.5\%$; C, $23 \pm 7\%$.

The relations of the cytoarchitectural areas to the sulci can be stated very briefly (see frontispiece): The central sulcus marks the posterior border of area 4γ. Area 4s lies close to the superior and inferior precentral sulci. The anterior border of area 6 is not marked by any sulcus As was mentioned before, the anterior border of area 44 appears to be marked by the diagonal sulcus.

Blood Supply

Blood is supplied to the precentral motor cortex in man by the anterior and the middle cerebral arteries (fig. 36). The former irrigates the cortex of the medial and of the uppermost part of the lateral side of the hemisphere, while the latter supplies blood to the rest of the lateral side

Blood brought by the anterior cerebral artery flows to the precentral motor cortex through the callosomarginal artery. The middle cerebral, or Sylvian, artery sends off several branches to that part of the cortex which interests us here. Levy (1927), whom Bailey (1933) followed, recognized an orbito-frontal, a pre-Rolandic, and a Rolandic branch (fig. 36; 1, 2, and 3 respectively) Testut (1929) describes an "anterior or inferior frontal," an "ascending frontal or prefrontal," and an "artery of the Rolandic fissure." This last one, he states, "reaches beyond the upper margin of the hemisphere."

The venous drainage (fig. 37) of the precentral motor cortex is effected in two ways. That part of the cortex which is supplied by the anterior cerebral artery sends its blood through small veins directly to the superior longitudinal sinus. That part which is supplied by the Sylvian artery sends its blood mainly into the great anastomotic vein of Trolard. This vein, which, for inexplicable reasons, has not received the sanction of official anatomical nomenclature, is described by Testut (1929) as running "along the posterior part of the ascending parietal gyrus" (i.e., the post-central gyrus). Bailey (1933), with a finer sense for organic variability, described it as running "vaguely in the direction of the central sulcus." The variations in the position of the vein of Trolard are well illustrated in Moniz' (1940) phlebograms.
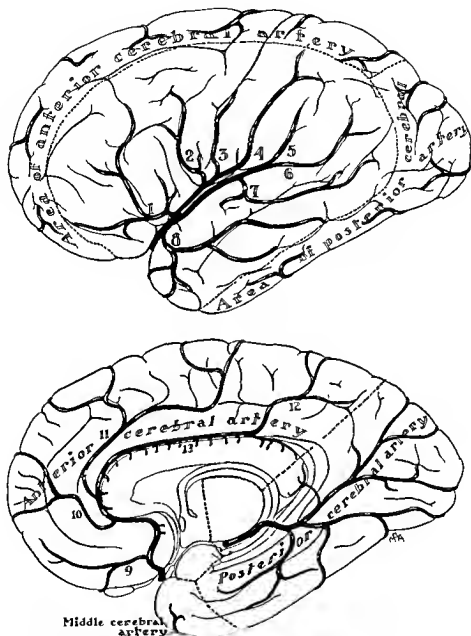
Fig 36 —Arterial supply of the cerebral cortex After P. Bailey (1933), by permission of the author and of the publisher, Charles C Thomas

Great anastomotic vein

Rolandic veins

Lat occipital veins

Frontal anasto-
motic vein

Middle cerebral vein

Small anastomotic vein

Median superior
cerebral veins

Great cere-
bral vein

Internal occip-
ital vein

Basilar vein
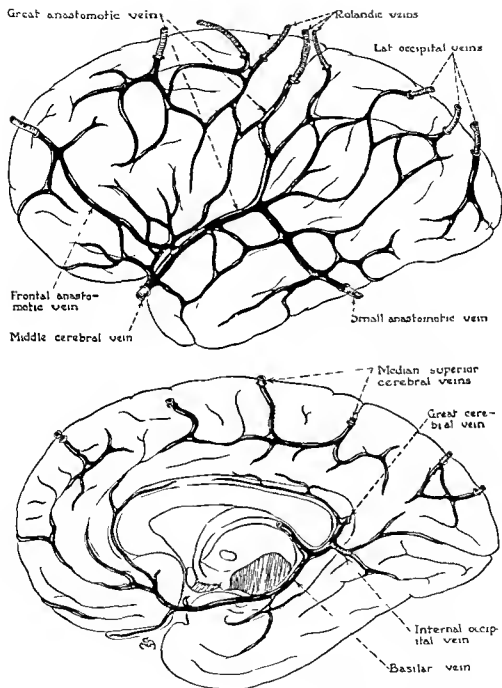
FIG 37—Veins of the cerebral cortex After P Bailey (1933), by permission of the author and of the publisher

PHYLOGENY

The material given above allows us to discuss some points of the comparative anatomy of the precentral motor cortex. To draw conclusions about phylogeny from a comparison of living forms is, of course, dangerous (see Bonin, 1945), as T. Edinger (1948) has shown in a concrete instance.

Cortical Architecture and Phylogenesis

It needs but a cursory glance at the photomicrographs (figs. 5, 10, 18, and 22) to see that the cell density of area 4 decreases progressively from monkey to man.

It has long been debated whether cell density is correlated with the level of organization of the brain.[4] From the point of view of communication engineering, the "level of organization" may be defined as a function of the number of different messages which the brain or the cortex could send out. Obviously, that number depends on the number of neurons and of the possible combinations between them. But this in turn depends on the degree of synchronization forced upon the individual cells by their neighbors, and according to our previous reasoning this may be a function of the cell density. An actual survey of many species, however, led Mayer (1912) to the conclusion that "the number of cells in the cortex is not an expression of the level of organization of the brain, nor can it be considered as a measure of the animal's intelligence."

Von Economo (1926), along with Nissl, held the opposite view and proposed his gray/cell coefficient. He defined it as the relation between the sum total of the cortical volume and the sum total of the cell volumes. The coefficient was actually given only for the human brain.

Agduhr (1941) pointed out serious technical shortcomings in von Economo's technique and gave a method for correcting them. Agduhr also objected to an overall coefficient for the entire cortex, and demanded individual coefficients for each layer of each area—a truly Herculean task.

Van Erp Taalman Kip (1938) determined in a satisfactory way[5] the relative cell density in selected areas of the cortex of rodents. The reciprocal of that quantity measures the average cortical volume at the disposal of one cell. He introduces the term "cell territory" for this quantity and shows that the cell territories change from animal to animal as the square root of the body length.

The concept of cell territory is hard to visualize. One has only to study

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[4] A short survey of the literature pertaining to this question was given by Bonin (1938).

[5] He measured the cells in sections of different and known thicknesses and computed his constants by subtracting the value found for the thinner section from that found for the thicker one.

a protoplasmic plexus to realize that a certain fraction of each cell territory is so hopelessly entangled with many others as to defy any simple analysis. Even the larger dendrites intertwine, with the result that the "local dendritic fields" frequently overlap. It seemed better, therefore, to restrict considerations to the cell bodies, and to follow von Economo, taking heed, however, of Agduhr's criticisms.

At present it is possible to report on only the fifth layer of area 4. The resulting gray/cell coefficients are given below. The table also contains data about brain weights, the authorities for which were cited in a previous publication (Bonin, 1937).

	Gray/Cell Coefficient	Brain Weight (in grams)
Galago	52	7 9
Macaque	87	86 0
Chimpanzee	112	400 0
Man	233	1400 0

Figure 38 shows a graph of these figures on a double logarithmic scale. In themselves insufficient, these results support Economo as well as our previous reasoning about cell density and level of organization.

A second point that can be observed by inspection and verified by actual measurements is the increase in the relative size of the giant cells of Betz during evolution The measurements given below for man, cebus, and the cat, taken from Bonin (1938b), represent nuclear volumes, expressed as cubic microns The measurements for the chimpanzee are in arbitrary units.

	Ordinary Cells	Giant Cells	Ratio
Man	371	2328	6 3
Chimpanzee	484	2450	5 1
Cebus	306	1131	3 7
Cat	441	1515	3 4

It has been pointed out by Bok (1936) that the surface of a cortical ganglion cell is proportional to its nuclear volume. Our figures would indicate that in more highly organized brains the Betz cells have a relatively greater number of axosomatic synapses than the "normal" population surrounding them, assuming, of course, that the number of synapses per unit surface area remains constant They accord well with von Economo's reasoning about the importance of neuronal connections for the level of cortical organization.

Lassek (1940, 1941b) has given us some information about the total number of giant cells within area 4 of the macaque and area 4γ of man (see pp. 17 and 41). These figures become of still greater interest if they are compared with the total volume of the areas in which they are lodged. The volume of area 4γ in man was given by Rose (1936), and it may be

assumed that his definition was comparable to the one adopted in this chapter. The volume of the macaque's area 4 was measured by the writer. A summary of these various measurements follows:

	Man	Macaque
Volume of area 4γ (cubic mm)	2,857	608
Total number of giant cells (Lassek)	34,370	18,854
Number of cells per cubic mm	12	31

The macaque has more than twice as many cells per unit volume as man. These overall measurements are, of course, necessarily crude. The detailed arrangement of the Betz cells, whether solitary, in nests, or multilaminar, has completely gone out of sight. Moreover, Lassek's work proves that the Betz cells are by no means the only ones giving rise to pyramidal fibers. So long as the origin and the termination of the pyramidal tract, as well as the numerical relation between pyramidal fibers and final common pathways are not known in all details, it is useless to speculate any further.

Fissures and Areas

Most authors appear to have given up the comparative morphology of the sulci as a hopeless task. Yet at least some sulci of the primate brain are obviously as constant as many other morphological features, and it is hard, moreover, to think of them as completely divorced from the pattern of cortical areas. It may be worthwhile, therefore, to reexamine this problem, less in order to solve it completely than to illuminate its peculiar difficulties.
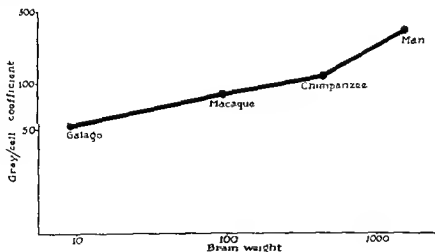
Fig. 38—Diagram showing the relations between brain weight and gray/cell coefficient. Double logarithmic scale.

For that purpose, it may be redefined as the problem of the homologies of the cerebral sulci. Yet the concept of "homology," although pivotal for all phylogenetic considerations, has never been rigorously defined. Even Woodger (1937) in his formal analysis of biology stopped short of this problem, contenting himself with a discussion in everyday language.

The confusion introduced into morphology by using the term homology in various senses may largely be responsible for the revolt against the "historicism" of the early Darwinian morphologists, such as Ray Lankaster, Haeckel, and Gegenbaur, to name but a few. Beyond somewhat vague topological relations, it is almost impossible to find in the older neurological literature a precise morphological criterion for the homology of the cerebral sulci. Is it possible to get beyond this impasse by taking into account the microscopic structure of the brain? On page 9 a cortical sector was defined by its thalamocortical connections, i.e., by its innervation. These relations should afford a valid and workable criterion of homology, at least so long as discourse is restricted to the primates. We agree with Le Gros Clark (1945) about "the futility of attempting to homologize sulci in widely different species."

Do cerebral sulci stand in definite relation to cortical areas? This has been denied by such competent neurologists as Arieus Kappers, O. Vogt, and von Economo. It is to be feared, however, that they went a little too far, for there are several sulci about which such relations have to be affirmed. The central, the calcarine, and the callosomarginal sulci are cases in point. The importance for cortical folding of the relative expansion of certain cortical areas during ontogenesis, and of the different thickness of the cortex in different areas has been made clear by Le Gros Clark (1945). As Elliot Smith has explained (1931), a sulcus may be either axial or limiting. We shall call homologous all limiting sulci which indicate the boundaries between homologous areas as well as all axial sulci situated within homologous areas.

It should be emphasized that the relationship between a sulcus and an areal boundary is not as sharply fixed as one might wish, for organisms are variable. Just as the size of the brain as a whole, or the cephalic index, or any other measurable character varies within a given sample of any species, so does the distance of a sulcus from an areal boundary. That does not preclude the use of average values for comparisons between different species. For a first orientation, it appears permissible to disregard minor variations. Otherwise we may not see the woods for the trees.

The evidence from alouatta (see fig. 6, p. 15) shows that the central sulcus and the posterior boundary of area 4 need not have very close rela-

tions with each other. The material gathered in Brodmann's (1912) report or in Huber's monograph (1934) shows, on the other hand, that the topographical discrepancies between boundary and sulcus are rarely very large. When we come to the cebus (fig. 8, p. 16) or the macaque (fig. 9, p. 17), the relation between areal boundary and sulcus has become much more intimate. For the greatest part of the sulcus, border line and furrow coincide. They diverge only at the dorsal and ventral ends of the sulcus. These divergences become still smaller in the chimpanzee (fig. 17, p. 27) and disappear completely in man (see frontispiece). In the case of the Rolandic sulcus, complete coincidence of areal boundary and sulcus is established only very gradually. Whether this observation can be generalized, is not clear *a priori*. Obviously, the central sulcus of the macaque should be considered only "roughly" homologous to that of man. By "roughly" is meant that its main body is homologous to the main body of the same sulcus in man, but that some part of it (it happens to be the ventral "bend", continuous, of course, with the rest of the furrow), does not correspond to any part of the human sulcus

The position of the precentral suppressor area, or the boundary between areas 4 and 6 is marked by the superior precentral sulcus in the dorsal part of the hemisphere, i.e., in the field for the leg and arm. It is but a small dimple in the macaque, but a constant and easily definable furrow in the chimpanzee and in man.

The boundary between areas 6 and 44 is indicated by the inferior precentral sulcus in man and by the anterior subcentral in the chimpanzee and macaque. The inferior precentral sulcus of man is therefore the homologon of the anterior subcentral sulcus of the chimpanzee and of the macaque

In the macaque the anterior boundary of area 6 is approximately marked by the arcuate sulcus. In both the chimpanzee and in man the anterior boundary of area 6 cuts right across the pattern of the frontal sulci in the dorsal part of the hemisphere.

The anterior boundary of area 44, on the other hand, is indicated in the chimpanzee by the fronto-orbital sulcus and in man by the diagonal sulcus of Eberstaller. In the human brain the vertical anterior ramus of the Sylvian fissure appears to be an axial sulcus of the frontal suppressor area. The macaque's inferior ramus of the arcuate sulcus may, therefore, be homologous to the frontal-orbital sulcus of the chimpanzee and the diagonal sulcus of Eberstaller in man. The change in the configuration of the sulcal pattern along the anterior border of area 44 is remarkable and clearly calls for further investigations. However, these homologies can be

definitely established only when we have more detailed information about the functional organization of the human brain.

Much of what has been written about cerebral sulci stands badly in need of revision. These brief remarks are merely intended to show that, by allowing for organic variability and by choosing the proper criterion, one can arrive at homologies of at least some of the cerebral sulci.

Progressive Differentiation and Use of Symbols

Another point that can be illustrated by a comparative study of the premotor cortex is the progressive differentiation which cortical areas undergo. Area 6, it is true, remains practically the same throughout the primates, but area 4 shows distinct changes from galago to man. A single area in the macaque, it has been shown (see Chapter VIII) to consist of two functionally distinct bands (IV and V, fig. 91b) in the chimpanzee. These bands can not be differentiated histologically in that primate. In man, on the other hand, a histological differentiation is possible within the arm and face fields. The two areas were recognized by von Economo and Koskinas as FAγ and FA, and we have tried to follow them by designating the areas as 4γ and 4a. Brodmann realized this process of progressive differentiation and discussed it at some length in Chapter VII of his well-known monograph (1909): "In many instances certain regions of more primitive mammals will have to be considered as oriments of the multitude of cortical areas into which they were split up."[*] Unfortunately, Brodmann's system of using the same numbers on all his brain maps did much to obscure this obvious principle. It is true, he points out again and again in the text, that merely using the same numbers in different animals does not imply strict homologies, but he evidently underrated the peculiar persuasive force of his symbols. The potential danger of this system became all the more real when his untimely death prevented him from publishing detailed cytoarchitectural analyses of man as well as of other animals. His last map of the human brain clearly shows that he was still revising his conceptions.

The problem of symbols is by no means easy to solve. Two systems compete with each other while still others, such as that of the Vogts, "also run." Brodmann's system of numbers is arbitrary and meaningless in itself. He simply called 1, 2, 3, 4 those areas which appeared in that order in a horizontal series when searched through dorsoventrally. But he certainly

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[*] . . . wird man vielfach gewisse oben beschriebene Regionen einfacherer organisierter Säugetiere als Primitivorgane der bei höherer Entwicklung vorhandenen Vielheit von Rindenfeldern, in welche die betreffende Region sich gespalten hat, bezeichnen müssen

did not stick to this principle, since area 19 must have appeared before
area 17. However, these are minor details. The great drawback of Brodmann's system is that it can not take care of progressive differentiation.
The other system is that of von Economo and Koskinas. It is more elaborate and withal more flexible. Its disadvantages are that it is less popular
and that it tends to perpetuate the outmoded division of the hemispheres
into lobes, against which a crusade becomes more and more imminent.[1]
We have decided, therefore, in favor of Brodmann's system, but have tried
to elaborate by tagging letters on to the numbers. In these days of symbolic
logic and precise symbolism it may be well for neurology to revise its system, too. The treatment of area 4 in this chapter can easily be applied to
other cortical areas.

Relative Size of Area 4

A glance at the maps of the precentral motor cortex given in figs. 5, 7,
18, 22, and the frontispiece will suffice to show that as we ascend the phylogenetic scale of the primates to man, area 4 becomes relatively smaller in
comparison with the rest of the precentral motor cortex. As mentioned
before, Rose (1936) gave some data for man, and these could be compared
with measurements which the writer made on the brain of a macaque cut
in serial sections. Rose's figures for area 6 are almost certainly too large,
since he included everything of the precentral motor cortex which was not
area 4γ. But even allowing some leeway, the difference between the monkey
and man is impressive. In the monkey, areas 4 and 6 are of about equal
size, while in man, area 6 is about six times as large as area 4γ, as shown by
the following figures:

	Macaque	Man
(a) Area 4 (cubic mm)	608	2,857
(b) Area 6 and area 44 (cubic mm)	638	17,243
Relative size of area 4—100a/(a+b)	48.8%	14.2%

Topological Relations

During phylogenesis the areas of the face field undergo a topological
rearrangement which may be of functional importance. Areas 4 and 6
reach much farther ventrad in man than they do in the macaque. Consequently, the border between area 44 and area 43, while present in the
macaque, is completely wiped out in man. The details of the areal pattern
on the Rolandic operculum of man vary quite widely, as von Economo

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[1] The writer has taken several opportunities of pointing to the need for an improved subdivision of the cortex (Bonin, 1941 and 1945, Bonin, Garol, and McCulloch, 1942). The same
need appears to be felt by Beck (1910).

(1930) showed. Yet this much can be said, that in man, area 6 elbowed its way down between area 43 and area 44. The broad "belt" of granular cortex covering the frontoparietal operculum in the cebus monkey (see Bonin, 1938a), as well as in the macaque, becomes narrower in the chimpanzee and is almost completely broken up in man. Without confirmatory evidence it is not permissible to transfer the "firing diagram" of the monkey (see Chapter VIII) to that which could be constructed for man.

Broca's Convolution

The homologies of the cortical areas advocated in this account are by no means entirely new, as must have been evident to the patient reader. It has merely been pieced together from several bits of evidence and has, after all, only confirmed assertions made by previous authors. So far as the writer can see, however, its implications have never been made clear. Broca, Bischoff, and a host of other writers repeatedly stated that the third frontal convolution was a specific human character and either did not exist in lower forms or was at least very rudimentary. Even as late as 1925, von Economo and Koskinas asserted that their area FCBm had "no homologon among animals, just as the macroscopic basis is missing in the animal kingdom (rudimentary or entirely missing third frontal convolution)." If the homologies advocated on these pages are accepted, the story reads quite differently. Area 44 is present in all primates, including cebus and macaque. In the macaque, its electrical stimulation yields movements of the vocal cords (see Sugar, Chusid, and French, 1948). In man it is recruited into the family of cortical areas which subserve articulate speech (see Thiele, 1928, p. 355). Exactly how it subserves speech is scarcely understood.

In the macaque, it has cortico-cortical connections with areas 4 and 43. Of the human brain we know nothing. Rasmussen and Penfield (1947) could throw normal flow of speech "out of gear" by electrical stimulation of areas 4 and 43, but not of area 44. Penfield and Boldrey (1937) obtained no movements or sensations from area 44. The exact homologue of Broca's convolution in subhuman primates still remains to be found.

SOME ADJACENT AREAS

Two areas of the frontal sector, namely the frontal suppressor area and the area orbitalis agranularis, as well as the anterior limbic area, require a short description. In order to be brief, we shall refer only casually to sub-

human forms, although their experimental study has furnished the most important clues, and confine ourselves mainly to the human brain.

Frontal Suppressor Area

A frontal suppressor area, defined physiologically by its property of suppressing motor responses and the electrical activity of the rest of the cortex, was found in both macaque and chimpanzee to extend in front of the precentral subsector over the whole lateral side of the hemisphere (cf. Chapter VIII). It is a comparatively narrow band, and forms part of the frontal oculomotor field (see Chapter XII).

The architecture of this band, however, is not uniform throughout its extent. In the macaque, it corresponds to Walker's (1940a) areas 8B, 8A, and 45 and to Bonin and Bailey's (1947) FC and FDΓ. Its ventral part contains large pyramidal cells in both layers III and V and is eugranular, while its dorsal part is tenuigranular. It may be inferred that the "frontal suppressor area" in the human brain consists of FC (fig. 39) as well as of either the anterior part of FCBm, or FDΓ (fig. 40) of von Economo and Koskinas. In Brodmann's nomenclature this would be area 8 and the most occipital part of 9, as well as 44a or 45. As has been said above, there are reasons to look upon the anterior part of FCBm as a suppressor area

For purposes of histological description we must subdivide the frontal suppressor area into a dorsal part, which we shall call area 8 and which coincides with von Economo's FC, and a ventral part to be referred to as area 45, following Brodmann. This amounts to an extension downward of Brodmann's area 8 of the human brain on the basis of von Economo's results (cf. figs. 2a and 3a).

Area 8—In area 8, the thickness of the cortex is less than in areas 4 and 6. It is hard to recognize this cytoarchitectural area in the myeloarchitectural maps of the human brain published by O. Vogt (1910) or by Strasburger (1937). Von Economo surmises that Vogt's areas 47, 46, and 55, and perhaps 36 and 45, belong to his area FC (which is our area 8). An examination of Strasburger's map makes it likely that 45 belongs to area 8, while 36 must remain doubtful. Strasburger illustrates the myeloarchitecture of areas 45, 47, and 55a, showing but slight differences between them. The most important thing to learn from these studies is that the outer stripe of Baillarger is broad and has a sharp inner, but a blurred outer, boundary. It is clear that what is conventionally called layer IIIc is still within the stripe of Baillarger. Some years ago, Lorente de Nó (1938a) was at great pains to point out that it was not certain whether the laminar pattern described by him for the parieto-temporo-occipital
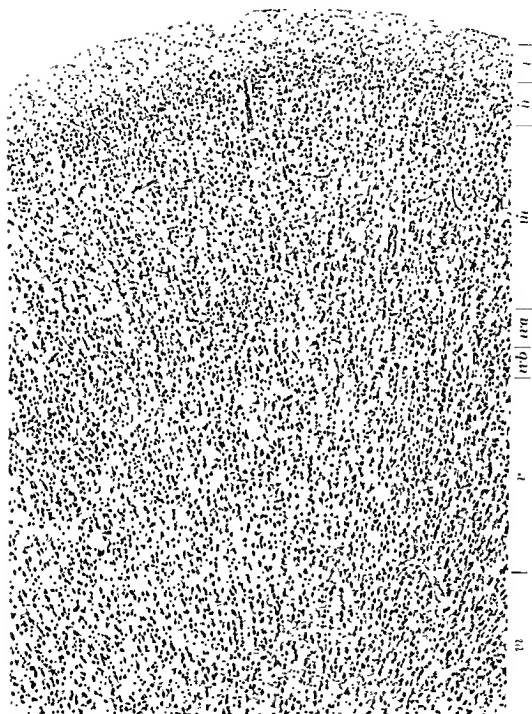
Fig. 39 — Dorsal part of area 8 of the human cortex. Toluidin blue. After von Economo and Koskinas (1925, plate XII). Magnification about 45 : 1
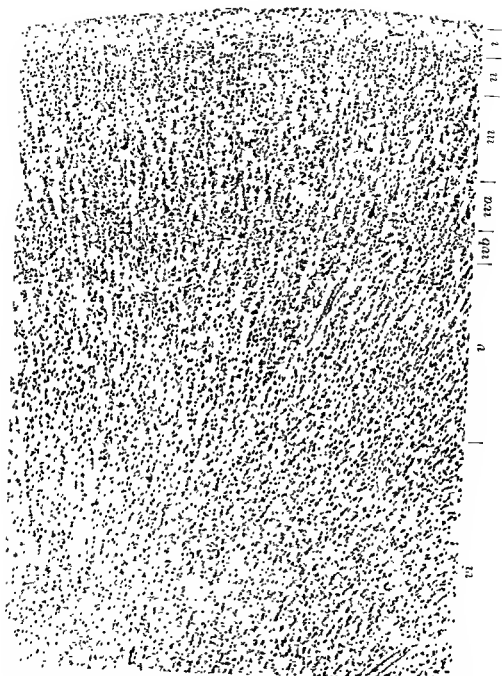
Fig. 40.—Area "FDf" of von Economo and Koskinas (cf. fig. 3.) Toluidin blue. After von Economo and Koskinas (1925, plate XXVIII). Magnification about 45:1. This may belong to the central part of area 8.

cortex was applicable to the frontal cortex as well. After comparing the myelo- and cytoarchitectural patterns of the frontal sector and after studying silver preparations, there seems no reason not to extend Lorente de Nó's fundamental scheme. We shall have to make an adjustment, however, by counting layer IIIc as layer *iva*, since it is definitely within the stripe of Baillarger. The cytoarchitectural structure then becomes easy to understand, and presents largely a repetition of what is found in other areas. The border between layers *ii* and *iii* is blurred. The third layer is broad and contains medium-sized pyramidal cells, which are larger in the deeper parts of that layer. Layer *iva* blends with the lowest part of layer *iii*. It contains pyramidal cells of about the same size as in the lower substratum of *iii*, interspersed with smaller granules. It is clearly delimited from layer *ivb*. That sublayer is thin, but well defined, and contains mostly granules and only occasionally larger pyramidal cells. The fifth layer can be subdivided into an upper substratum containing comparatively few and small cells, a middle layer containing larger pyramidal cells, evidently of the efferent type, and a lower sublayer more sparsely filled with cells which are either pyramidal or triangular. The upper substratum is correctly indicated by von Economo and Koskinas on their plate XIII. The distinction between layers *vb* and *vc*, however, is not drawn. The sixth layer contains polymorph cells; it represents nothing unusual. The border against the white matter is not very sharp, although more distinct than in the motor cortex.

Area 45 or FDΓ is one of the most easily identifiable areas in the primate brain. It has been found in Hapale (Peden and Bonin, 1947). It has, upon reexamination, been identified in the cebus (it was overlooked by Bonin in 1938a). Bonin and Bailey (1947) described it in the macaque on the anterior lip of the lower branch of the arcuate sulcus, and it is easily found in the chimpanzee. In the macaque, Chusid, Sugar, and French (1948) have investigated its cortico-cortical connections (see Chapter VIII) and have observed the effect of its stimulation upon ocular movements.

The homology with the human area FDΓ rests at the moment entirely on cytoarchitectural resemblances since nothing appears to be known of the function or the results of stimulation of that area in man.

According to von Economo and Koskinas, area FDΓ is much thinner than the adjacent regions, has a more pronounced lamination and columnization, a much lighter fifth layer, and conspicuously large pyramidal cells in the lowest reaches of the third layer (which appears to be layer IVa). Myeloarchitecturally it shows (cf. von Economo and Koskinas, 1925, *loc. cit.* fig. 123, p. 360) a confluence of the inner and outer stripes of Baillarger (unitostriate type).

Area Orbitalis Agranularis

The orbital agranular area was considered by Campbell (1905, plate XXII) as a part of the "intermediate precentral" cortex, and by von Economo and Koskinas (1925) as FFa (fig 3a). Brodmann indicated it on his map (fig. 2a) of the human brain as 47, but failed to show it in subhuman brains. It was also overlooked by Bonin (1938a) in his description of the brain of the cebus Walker (1940a) described it recently in the macaque as area 13 He pointed out that Spencer, and Bailey and Sweet had obtained respiratory arrest by electrical stimulation of this area and that it was evidently the homologon of this area in the cat from which Bailey and Bremer had obtained action currents upon stimulation of the vagus. Walker's nomenclature is apt to cause confusion, since Brodmann (1909) used the number 13 for an area of the island of Reil in Hapale, lemur, and other mammals Bonin and Bailey (1947) described it as area FF in the macaque. Meyer, Beck, and McLardy (1947) appear to consider the medial part of the orbital cortex, i.e., Brodmann's area 11 as the homologon of that area in the macaque on which Bailey and Sweet (1940) worked. They state that this area receives thalamic afferents from the magnocellular portion of the medial nucleus. While the question can be definitely settled only by direct observations, the relations of area 47 to the orbital sulci as well as the cytoarchitectural characteristics strongly suggest the homology adopted here.

Area 47 was considered to belong to the "infrafrontal" region by Brodmann (1914) and, what amounts to the same thing, to the "wider area of Broca" by Kreht and Strasburger. From Kreht's cytoarchitectural studies his fields 61, 62, 63, and 66, and perhaps 64 appear to belong to Brodmann's area 47 Strasburger described 61 and 62 as bistriate, and 63 and 66 as unitostriate The photographs accompanying his later paper, however, show comparatively little difference between all these areas.

In man, area 47 (fig 41) is characterized by small cells throughout. The border between the second and the third layer is distinct. The size of the pyramidal cells in the lower parts of the third layer is not much greater than in its upper part. The fourth layer which we define again as that stratum which contains the outer stripe of Baillarger, contains mostly large cells spaced about as far apart as in the lower part of the third layer. A cell stain will, therefore, frequently fail to show a definite fourth or "granular" layer. Hence the name area orbitalis agranularis. Von Economo and Koskinas mention, however, that in some individuals the fourth layer contains densely packed granules, forming a conspicuous layer in cell preparations The fifth layer contains again only small cells and can not easily

Fig. 41 —Area 47 of the human brain. Toluidin blue. After von Economo and Koskinas (1925, plate XXXIII). Magnification about 45:1

be subdivided into sublayers. The sixth layer contains small fusiform cells; the border against the white matter is fairly sharp.

Area 47 is present in all mammals thus far investigated, e.g., in the chimpanzee, the macaque (cf. fig. 9, p. 17), and the cat. The conception expressed by Brodmann in his nomenclature can therefore not be upheld. Brodmann was evidently influenced by the teachings of Broca and many others, who, it will be recalled, held that the third frontal convolution on the orbital part of which area 47 is situated was a new phylogenetical acquisition characteristic of the human brain. What was more natural than to assume that the cytoarchitectural areas covering man's inferior frontal convolution had no homologon in lowly beasts!

Anterior Limbic Area

Area 24—The anterior limbic area (fig. 42) was not recognized by Campbell. The first to describe it and to show its position was Brodmann (cf. fig. 2b), who gave it the number 24. Von Economo and Koskinas (fig. 3b) designated it as LA, and subdivided it further into LA1, LA2, and LA3. The area was studied in detail by Rose (1928).

Recent experiments on the chimpanzee by Bailey *et al.* (1944) and on the macaque by W. K Smith (1945) have shown that area 24 is a suppressor area. Smith observed in addition a complex response (opening of eyes, dilatation of pupils, etc.) bearing "the connotation of emotional expression."

Through embryological studies, Rose (1926) came to the conclusion that the cortex of the anterior cingular area, as well as that of two areas in the retrosplenial region, differed fundamentally from the rest of the cortex in its pattern of stratification. The isocortex proper was, in Rose's terminology, a cortex holoprototychos septemstratificatus. The area just mentioned he described as cortex holoprototychos quinquestratificatus, or, for short, as mesocortex. The three areas bear mesocortex of different type. To Brodmann's area 24 he applied the myeloarchitectural term regio infraradiata. Brodmann's 30 he called regio retrosplenialis agranularis, and area 29 regio retrosplenialis granularis. The mesocortex was studied by Rose (1928) in marsupials, some lower mammals, the lemur, the chimpanzee and man. In the lower mammals, as well as in the lemur, the mesocortex covers the whole gyrus cinguli and is continuous posteriorly with the retrosplenial region. In the two higher primates, the regio infraradiata is divided from the retrosplenial formations by a wide expanse of isocortex covering the posterior part of the gyrus cinguli. It may be added that this holds true also for the macaque (Bonin and Bailey, 1947), for the
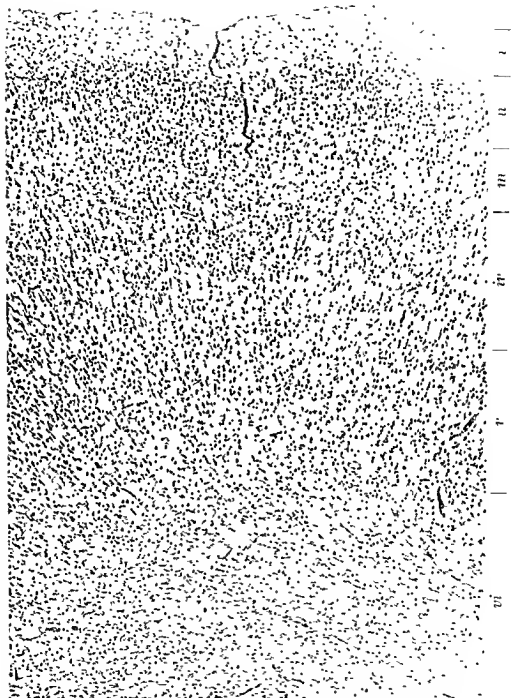
Fig 42—Area 21 of the human brain Toluidin blue After von Economo and Koskinas (1925, plate XLV) Magnification about 45·1

cercopithecus (Brodmann, 1909), and for the cebus (Bonin, 1938a). In the primates, as Rose states, "the gyrus cinguli is not architecturally homogeneous." The photomicrographs of the anterior limbic area published by Rose suggest a remarkable constancy of its architecture from mouse to man.

Mention should finally be made of a long and narrow strip of cortex, hidden in the macaque and the chimpanzee for a large part in the depth of the sulcus cinguli. By the method of physiological neuronography it was found that this area receives association fibers from all the suppressor areas of the cortex (see Chapter VIII)

In man, this area appears to correspond to Brodmann's areas 32 and 31, with the proviso, however, that these two areas are contiguous, probably in the depth of the sulcus. Areas 32 and 31 obviously differ histologically from each other, and the intervening part may also have other characteristics. But a more thorough study of this part of the cortex has to be postponed.

EPILOGUE

We are at the end of our survey. To the reader who has had patience enough to work his way through this chapter, it will have become clear that the description of the precentral cortex presented on the foregoing pages differs from that found in previous texts. The writer hopes to have made clear his reasons for this deviation from tradition. The conception of the precentral motor cortex expounded here rests on three lines of evidence: (1) on the architecture of the cortex, (2) on our knowledge of subhuman primate brains, and (3) on physiological observations. The last point is particularly important for the suppressor areas Our conception is hypothetical insofar as it presupposes that all primate brains exhibit the same fundamental pattern Hypotheses are of scientific value only when there is a method of testing them That should be possible in our case, but it is clearly the task of the neurosurgeon who alone enjoys the privilege of observing the living human brain

To the extent to which our views may be accepted by the clinician as a challenge, and may lead to eventual clarification, this chapter will have contributed to clinical medicine.[*]

In a few places we have indulged in speculations about cortical activity, for the dry details of histology are lifted above the rank of "vacuous acuity" only when they can be made to contribute to our understanding

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[*] On August 3 1913 Bucy was able to demonstrate in the human being relaxation of muscular contraction and abolition of after-discharge by stimulating the anterior lip of the superior precentral sulcus where area 4s was presumed to be situated (cf p 51)

of cortical function. The most important question that could be discussed was whether a "field," in the sense in which the theory of isomorphism uses that term, can be established or whether cortical events remain individualized, not whether cortical activity was motor or sensory or chalastic, i.e., suppressing. This generalization may be made therefore: *What* the cortex does, is determined by its connections with the rest of the central nervous system; *how* the cortex does it, depends on its histological structure, on what is commonly known as its architecture. There is no way, at least so far as the writer can see, to check hypotheses of cortical activity by experiments. The only way which promises progress is to work out a formal theory taking into account the degree to which the cortical substrate approximates that required for a field and to test the consequences in the light of observable facts But this should be left to others better trained in theorizing.

To the extent to which this task will be undertaken, this chapter will have contributed to our understanding of cortical activity.

The approach from comparative anatomy led to a conception of the evolution of the human brain differing in at least one important aspect from previous attempts. It concerns the third frontal convolution. Its opercular part, which bears the "motor speech center" of Broca, appears to be an old constituent of the primate brain and its orbital part, which bears area 47 of Brodmann, is at least equally old if not older. This result should lead to a revision of the conception of the frontal lobe. But we shall also arrive at different conceptions concerning the origin of language depending on whether we look upon man's speech center as something of recent or of ancient phylogenetic origin. If the latter alternative is accepted, it could be argued that the transition from the simple movements of larynx, tongue, etc., of which a beast is capable to the finely adjusted muscular activity of speaking (and singing) man requires first and foremost a sufficient expanse of the cortical territory mediating their nervous control The acquisition of language could then be linked with the increase of the size of the brain. Further elaborations are undoubtedly needed But speculations (or should we say reasonings?) about evolutionary processes are by their very nature unverifiable and therefore almost beyond the pale of science. Morphological discussions suffer, as we saw, from the lack of a clear definition of their central concept, that of homology. The attempt has been made to supply a criterion for homology by using the afferent connections of cortical areas. It has been tried in a very limited field only, and much more has to be done before it can be finally adjudged.

To the extent to which this criterion of homology will prove useful, this chapter will have contributed to the morphology of the primate brain.

Acknowledgment

Chapter III

THE ROLE OF ARCHITECTONICS IN DECIPHERING THE ELECTRICAL ACTIVITY OF THE CORTEX

James L. O'Leary, Ph.D., M.D.

Professor of Neurology, Washington University
School of Medicine, St. Louis

OUTLINE OF CHAPTER III

Architectonics and Electrical Activity

Acknowledgment

ARCHITECTONICS AND ELECTRICAL ACTIVITY

THE ELECTRICAL ACTIVITY of the nervous system is manifest as differences in potential which develop coincident to functioning. From the signs of function which can be recorded from the peripheral nerve to those which express the activity of the precentral cortex is a very long step as viewed in terms of the relative complexities of the anatomical substrates involved. Yet the axonal elements of the cortical pattern are the only ones with which the electrophysiologist is passably familiar; and if he is willing to ignore cell bodies and dendrites to the extent of representing them as modified axons, he may consider records of cortical activity as those of summed axonal elements functioning in parallel circuits. His knowledge of how to interpret the form of cortical records, then, stems back to the peripheral nerve through the various complications incurred in analyzing records from linear tracts of the CNS. Those other complications of electrical records for which cell bodies and dendrites may be responsible can only be interpreted after the various patterns of summed axonal records have been studied.

The potentials of the CNS may be recorded as "spontaneously" fluctuating changes of different amplitudes, polarities, and frequencies (Berger, 1929; Adrian and Matthews, 1934; and others), or may be induced by the natural stimulation of sense organs (Bartley, 1934; Marshall, Woolsey, and Bard, 1937 and 1938) or by electrical stimulation of nerves or pathways leading from sense organs to the region of the nervous system under investigation (Bartley and Bishop, 1933; Heinbecker and Bartley, 1940) In the analysis of records of activity the electrical stimulation of the nerve or tract activating a part of the nervous system has the obvious advantage that with a sufficient stimulus the elements thereof fire simultaneously, and the intervals between successive stimuli may be timed either to coincide with or to fall between the fluctuations of "spontaneous" activity. We may thus observe a record of many units responding in parallel, and consider that the form of this record is the same as that for the unit except in amplitude.

Thorough study of the processes of excitation and conduction in the nerve preceded the investigation of electrical activity of the CNS; and the first correlations between histological characteristics and electrical records became known through the identification of rapidly conducting components of the nerve potential with fibers of larger diameter, the slowly conducting components with fibers of lesser diameter (Gasser and Erlanger, 1927; Bishop and Heinbecker, 1930). The same correlation is demonstrable

in certain tracts of the CNS in which uniformly oriented axons of different dimensions occur (Bishop, 1933); but as these tracts enter the synaptic centers where they branch dichotomously, or change in calibre and terminate synaptically in relation to other neurons, new problems arise in the interpretation of electrical records. These problems are in part the general ones which deal with influences that modify the form of the potential record obtained from any active tract embedded in inactive tissue or other electrolytically conducting material. In part they are specific and relate to: (1) how the morphological configurations of different centers influence the potential records obtained therefrom; (2) what parts (axon, dendrite, or cell body) of the neuron are active in producing the different components of electrical records. If the nature of the general problems is understood, the solution of the specific ones can be approached by seeking the characteristics of electrical records and of histological structure in the different centers and attempting to relate the correspondences or lack of them that occur.

The subsequent account commences with the description of the form of action potentials in the peripheral nerve and the various modifications of these which may be encountered in recording from linear tracts of the CNS. These data provide the basis for considering the changes in the form of the electrical record which ensues as an electrode passes through a layer containing presynaptic terminals, synapses, and closely aggregated cell bodies and dendrites (lateral geniculate nucleus). Then the known facts of cortical architecture which appear to have significance in the interpretation of electrical records of cortical activity are presented in such a way as to avoid references to specific architectonic fields. This has been done to emphasize that, in so far as we now know, the forms of cortical records from different fields do not differ sufficiently to suggest that an analysis can now be attempted in terms of the specific morphological traits which differentiate one field from another. The application of the morphological data to the interpretation of cortical potentials is also considered as a whole, placing special emphasis on the area striata of the cat, the area with which the author is most familiar. The results of the application show what has been accomplished and what are likely to be the fruitful channels for investigation of the precentral cortex.

Record of Activity in Linear Tracts[1]

In general an "active" region of a nerve element is negative in potential sign relative to inactive regions on either side of the active point.

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[1] A technical discussion of these problems in terms of the membrane theory is to be found in an article by G. H. Bishop in the *Arch. Int. de Physiol.*, 1937, vol. 45, pp. 273-97. It is entitled "La théorie des circuits locaux permet-elle de prévoir la forme du potentiel d'action?"

The propagation of this activity, electrical or otherwise, along a nerve axon constitutes the nerve impulse. If each of two recording electrodes is close to a pathway, over which a nerve impulse is propagating, they become negative one to the other successively as the impulse arrives first at one and then at the other (fig. 43). The record of such activity is diphasic; and the "potential" observed is, of course, merely the curve of physical difference of potential between the electrodes, whatever their spatial relationship to the pathway. In the simple case of an isolated nerve suspended in air each phase can be assigned to its proper electrode as a physical sign of physiological activity occurring at that electrode. However, in recording from intact fibers embedded in a mass of active nervous tissue this simple situation is rarely met; activity may occur near both electrodes or between them, and the simple physical datum of a difference of potential is not sufficient to give the physiological information desired, i.e. where the source of potential is and what is the significant form of the underlying activity.

In such recording from the CNS the attempt is customarily made to place one electrode at an "indifferent" point, in the naive supposition that the electrical sign of activity can thus be imputed to the locus of the other electrode. In the case of linear excised nerve trunks suspended in air this is a satisfactory expedient, and killing the nerve under one electrode leaves a record chiefly of the activity in the vicinity of the other. However, such an interpretation is not generally feasible in three-dimensional systems such as are encountered in the CNS. One does not usually wish to kill any part of the pathway that is being studied, and even doing so would not result in simple records assignable to one electrode region. Activity at any
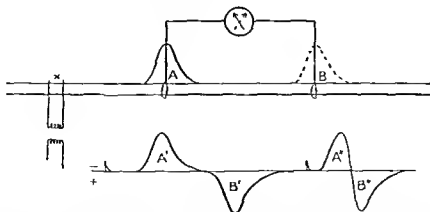
Fig. 43—The conventional scheme for recording linear stretches of nerve in air. Arising at the stimulated point X, the impulse arrives successively at A and B, the loci of two electrodes connected through a recording device. The identical form of activity is recorded as deflections of opposite polarities at A and B, as indicated in $A'B'$. If the conduction time between A and B is short, the two waves will be partially superimposed, as $A''B''$.

region sets up currents that flow through other regions, and both electrodes, wherever they are placed, may in general be within the physically conducting field of activity. The form of the record of even the simplest activity then depends upon the positions the electrodes occupy in this field.

Instead of a simple diphasic record, a double triphasic one is the most generalized type to be recorded from a three-dimensional system such as occurs in the CNS. It is not usually recorded in pure form; but other forms (fig. 44) which are recorded can often be understood as modifications of this basic type, and it is the modifications which give the clue as to the type and locus of activity. The double triphasic record may be expected
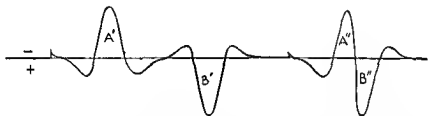
Fig 44—The result, comparable to fig 43, of the nerve being immersed in a conducting medium instead of being laid across electrodes in air Each phase of the diphasic $A'B'$ of fig 1 becomes itself a triphasic figure In $A''B''$ the conduction time is assumed to be such that the first positive deflection of B coincides with the negative deflection of A See fig 45

wherever activity is recorded from two electrodes both of which are in contact with a linear conducting bundle of fibers embedded in inactive tissue or other electrolytically conducting material. This happens when two needle electrodes are so inserted into brain substance as to make contact with a specific linear tract such as the optic tract (see p. 89) During activity current flows from each side of an active region, passing outside each fiber through the inactive tissue which surrounds the tract and back to its point of origin (fig. 45). Some branch of the external current flows past one or each electrode as the impulse arrives in its vicinity. As the impulse approaches it the electrode lies in a part of the field which is relatively positive; as the impulse passes under the electrode a more negative region of the field propagating with the impulse surrounds the electrode; and as the impulse recedes beyond the electrode the first condition is repeated in reverse order. The resultant plus-minus-plus deflection in the record corresponds to the arrival at the electrode of these three regions of the propagating field and not to the arrival of the impulse itself; the phenomena are repeated with propagation to the other electrode as minus-plus-minus deflections. These two triphasic series appear in the records with opposite signs because of the opposite relations of the two electrodes

to the recording device, even if the actual conditions under the two electrodes are identical.

In practice these simple relations are modified by so many factors that a simple triphasic record is rarely observed. The region of the field ahead of an impulse may be definitely positive relative to a region of activity but negative to a region further away (for example, to the region of the other electrode) so that no noticeable positive deflection appears in the record. The apparent start of the record is, however, affected, and the form of the deflection is not an accurate measure of the impulse at a point. Asymmetrical shunting of an active pathway, such as occurs when it lies close to and parallel to a surface of the tissue mass in which it is embedded (it may be subject to air insulation as are the superficial tracts of the exposed spinal cord), accentuates the positive phases of the record. Curvature of
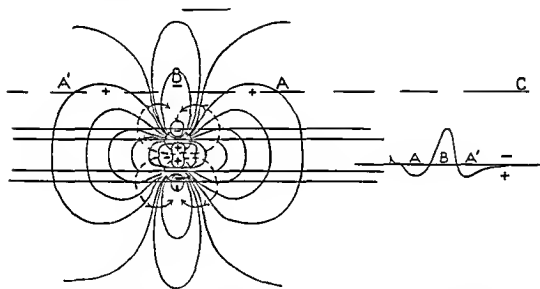
Fig 45 —Theoretical form of the potential field about an impulse in a linear element immersed in a conducting medium, represented in two dimensions only. Branches of the current from plus to minus flow in the external medium from A and A' toward B, current flow lines indicated by dash circles and arrows. The lines of equal potential in such a field cross the current flow lines at right angles, as indicated by full contour lines. This whole potential field may be thought of as propagating with the impulse, from the direction of A' to C. If electrodes are placed at A and C, the electrode at A will become successively positive, negative, and positive to that at C, as this electrode occupies the positions A, B, and A' with respect to the field. As the impulse passes C the record will be repeated with opposite polarity, as in $A'B'$ of fig 44. Note that maximum positivity is recorded where one of the isopotential lines is tangent to the line between electrodes. It is obvious from the figure that the further literally the electrodes are placed from the active element out in the medium, the greater the time elapsing between maximum positivity and maximum negativity. That is, the form and time relations of the record depend in general on the spatial relations of the electrodes to the tissue.
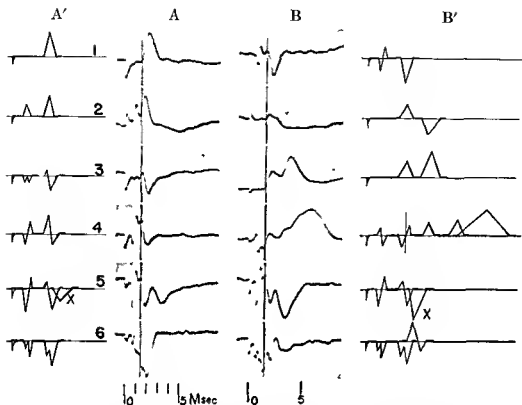
FIG 46—Records of linear tracts of the CNS of the cat. For each record the optic nerve was given a single stimulus in the eye socket One recording electrode (# 2 in fig 47) was placed just beneath the lateral geniculate nucleus, one (# 3) in the subcortical white matter below the medial suprasylvian gyrus, and one (# 1) was passed by 1-mm steps on a slant from the optic cortex covering the lateral gyrus downward and laterally toward the lateral geniculate nucleus. Each record was obtained by employing the movable electrode and one of the fixed electrodes as leads Except for records involving the striate cortex, B2, 3, and 4, each figure represents the responses of either the optic tract or the optic radiation or both, the various forms depending upon the positions of the electrodes The first deflection in each record is the disturbance caused by the shock at the eye socket A perpendicular line is drawn through the start of the optic radiation response at the cortical level, the response is slightly earlier at the geniculate

A1, optic radiation only, # 1 electrode above hippocampus, A2, 1st wave of this record optic tract, 2nd, radiation, recorded near geniculate, A3 and A4 same electrode entering geniculate, A5, the electrode reaches a bundle of optic tract fibers which do not activate the radiation (they have a higher threshold and slower conduction rate and are recorded as a separate later wave) In B5, a stronger stimulus activates more of these slow fibers A6, the first tract response and the radiation response, deeper in the geniculate, and B6, the addition of the later tract wave reversed in polarity at this level

B1 1st optic tract wave and radiation response, B2, radiation and first cortical neuron, B3 same higher in cortex, B4, response of the geniculate, tract and radiation, plus cortical response obtained from one electrode below the geniculate, and one on the surface of the striate cortex The diphasic process through which the vertical line passes is the radiation response recorded at each electrode Both electrodes are therefore beyond the terminations of the radiation fibers, each records a positive deflection when the impulse occupies the adjacent end of the pathway between electrodes (After Bishop and O'Leary, 1942)
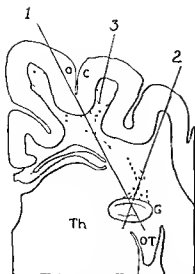
Fig 47 —Transverse section of cat's brain through the caudal level of the lateral geniculate nucleus (G) and the anterior region of the visual cortex (OC) indicating the electrode positions for records of fig 46 *1*, track of electrode passed by steps from the cortex to the geniculate, cutting the optic radiation (dotted lines) as the latter condenses into a bundle about half way down; below this the radiation passes anterior to the track of the electrode, *2*, electrode below the dorsal nucleus of the lateral geniculate body, *3*, electrode in white substance below supraylvian gyrus, *Th*, thalamus, *OT*, optic tract to lateral geniculate nucleus and superior colliculus (After Bishop and O'Leary, 1942)

the pathway with reference to a line between the electrodes is another type of asymmetry frequently encountered that affects the form of the record. When a pathway ends at synapses, one electrode being situated in the presynaptic region and the other beyond the synapses, the second triphasic complex is of course absent, although a modified record of the activity at the synapse may be obtained. The development of the third or final positive phase of the first complex then depends on the conducting distance from the electrode on the tract to the synaptic endings. When the electrode is close to this region the final positive phase is absent and a plus-minus diphasic record results. Various forms of the records of relatively simple CNS responses are presented in fig. 46, with arrangements as in fig 47.

Other modifications result from the variable distance at which an electrode may be situated relative to the active tissue. The record from an electrode decreases in amplitude with greater distance, and the relative prominence of positive and negative phases is also affected. Insertion of an *electrode into the center of an active tract (among its fibers) should in-* crease the negative deflection and decrease the positive, except that the unavoidable killing of tissue about the electrode tends to reverse the negative phase itself, making this electrode relatively positive to the active tissue around it. The system then acts as if the activity were at the other electrode, at whatever distance it may be from the locus of activity, in the sense that the distant electrode becomes relatively negative.

These generalizations concerning the expected form of records of activity from linear tracts are exemplified when the optic tract of the cat is recorded from the vicinity of the lateral geniculate body. Under light Nembutal anesthesia (0.25 to 0.35 cc. per kilo), supplemented by ether during the

period of preparation, a micrometrically controlled needle electrode insulated to within 0.5 mm of the tip is thrust directly into the tract and records are taken at various depths. The tract is activated by brief electric shocks applied to the contralateral optic nerve and the *critical needle*

tip is directed into the tract and recorded interchangeably against one of three distant *reference* needle electrodes One of these is placed caudal and ventral to the tract in the medial geniculate nucleus, another in the medial area of the thalamus, and the third in the caudate nucleus

Two axon waves, assignable to faster and slower fibers (in the recorded range) may be recognized anywhere in the brain stem, even in regions occupied by the optic radiation (Bishop and O'Leary, 1942) This is presumably due to the fact that the contra- and homolateral tracts form an almost complete circle about the brain stem Under the conditions of recording cited above the three *reference* electrodes occupy nearly isopotential positions in the field, and the *critical* electrode yields a positive spike corresponding to activity in the optic tract when the needle is in the optic radiation When inserted into the tract, di- or triphasic records result, the positive phases representing activity at other regions than the electrode That the record is strongly negative for the fibers with which the elec-

trode is in immediate contact is demonstrable by recourse to a fortunate anatomical consideration based upon the segregation of axons within the tract As the tract approaches the lateral geniculate body the larger axons separate to enter the dorsal nucleus, whereas the smaller ones turn toward the superior colliculus As the needle passes into the tract it may record the first tract spike as a predominantly negative wave, due to the fact that the electrode tip is in contact with the larger axons, whereas the second tract spike is recorded triphasically because the electrode has not yet made contact with the smaller axons As the needle tip passes deeper, so that it is in contact with the smaller axons, the condition is reversed, and the first tract spike as a strongly negative deflection The repetition of observations of this character in parallel experiments histologically controlled emphasizes for an anatomically simple case the way in which the functional correlates of histological structure may yet be obtained in the CNS

Partial Synchronism of Discharging Elements

In recording from the CNS, the different elements active in a tissue are not necessarily, or usually, synchronized, as has been assumed above. Larger axons conduct more rapidly than smaller ones, and even if all are stimulated together the impulses may arrive at a recording lead out of step with each other Negative phases of some elements will then coincide with the positive phases of others, and since the negative phases should in general be greater in potential-time area, the result can be a simple deflection of longer duration than the simple impulse in any one element would give rise to Furthermore, if sense organs instead of axon pathways are
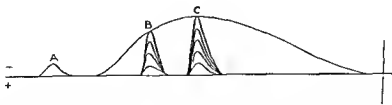
Fig 48 —A represents the form in which a single unit of a tract might be recorded by suitably placed electrodes, as a monophasic wave. It is assumed that the number of units responding increases with time, then falls off again, such that 4 respond at B, 5 at C, etc The long wave then represents the summation record of all the responses in a burst, assuming that the individual responses overlap smoothly The form of the overall curve is a measure of the time course of the total discharge rather than of the responses of the units It is possible that the cortical *alpha* wave signalizes such a burst of many discharges, repeated periodically

stimulated (Bartley and Bishop, 1942) or if "spontaneous" activity is being recorded, anything may occur, from a completely random activity to the degree of synchronism occasioned by the mutual facilitation of parallel elements, a phenomenon that can in fact occur at synaptic regions. The limit of completely random activity may result in a constant record showing no activity at all, and **to the degree that activity is asynchronous, the record is an unreliable measure of the activity giving rise to it.** For this reason, if for no others, the interpretation of CNS records is much more precarious and requires information of physical, histological, and physiological character concerning the precise conditions of activation in each experimental case. This has led the workers in our laboratory to place most reliance upon *induced* activity in seeking histological correlates with the form of electrical records.

An interesting special case is that of "modulation" of frequency in the activated elements; that is, the number responding per unit time increases and decreases rhythmically (fig. 48). This is probably a fundamental
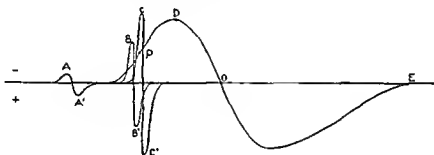
Fig 49—*AA'* represents, as *A* in fig 48 the response of a single unit but here recorded diphasically It is assumed again that the number of responses at each instant increases with time, then decreases Initially the sum of all the first phases at *C* will be greater than the sum of all the second phases, *B'*, at that instant, since the second phases are those following the smaller number of first phases recorded just previously The algebraic sum of *B'C* gives the amplitude of the overall curve at the point *P* When the number of unit responses is at its maximum (or becomes constant per unit time) the number of first and second phases is equal, their sum is zero, and the overall curve passes through the base line (*O*) The point *D* represents the time when the *increase* in number of responses per unit time is greatest, that is, when the excess of first phases over second phases is maximal Beyond *O* the conditions are reversed

In terms of frequency of individual discharges, the frequency increases to *O*, at an increasing rate to *D* and at a decreasing rate from *D* to *O* Beyond *O* the frequency decreases to *E* in reverse order If the two phases of the unit record *AA'* are not equal the form of the overall curve is obviously different but the same principle of summation apply

Either fig 48 or 49, repeated periodically, might offer an explanation of the spontaneous alpha rhythm of the brain, in which numerous individual responses may occur in successive bursts. However, according to the scheme of fig 48 the maxima and minima of the overall curve would represent the times of greatest and least activity, respectively, while according to the scheme of fig 49 the maxima and minima would represent times of greatest acceleration and deceleration of activity, with maximal and minimal *activity* halfway up and down between deflections The form of response of the unit element of the alpha process is not yet known.

characteristic of such activity as that exhibited in the *alpha* rhythm of the brain. The form of the record may then become a better measure of the frequency of unit responses than of the form of the individual unit's activity; the largest amplitude will represent the summation of the greatest number of individual responses at a given instant, the lowest amplitude the summation of the least number. The latter may be by no means zero. This is only true, however, if the record of the responses of an individual element would have been monophasic. If the arrangements of recording are such that the record of an individual response should have been diphasic with both phases equal, the amplitude of the summated record becomes a measure of the change in frequency of unit responses rather than a simple measure of their number per unit time (fig. 49). The maximum amplitude of the record then signalizes the period of greatest *increase* in frequency, and when that frequency becomes constant the deflection returns to the base line, since all the phases of one sign then just compensate all the phases of the other. A *decrease* of frequency would then cause an overall summated deflection in the opposite direction, since now fewer first phases are being recorded than second phases at a given instant, the second phases at that instant being those which follow first phases that occurred earlier when the frequency was greater.

Effect of Branching and Termination of Fibers

The above cited cases refer only to a uniform nervous pathway, that is, to one in which the number of axons and the character of the response of each axon do not vary along the pathway from point to point. This is unusual in the CNS. Pathways branch; collaterals of the contained axons terminate along them; and arborizations occur in the vicinity of synapses; and neurons consist of cells and dendrites as well as axons. Theoretical expectations and specific examples may be cited to illustrate how such factors influence the interpretation of records.

If all the axons in a pathway bifurcated in a given region, this would double the number of active units proceeding in one direction from that point. With successive dichotomous division the number would be still further increased. If the branching is a prelude to synaptic termination, a further complication in recording is introduced. The effects of branching and of synaptic ending might indeed be of opposite polarity, depending upon unpredictable factors such as the position of the critical electrode within the synaptic layer. However, the distances for conduction are so short that these effects might to all intents and purposes be simultaneous, that is, occur in such close succession that their records would nearly summate or perhaps give rise to a rapid diphasic deflection.

The central optic pathway of the cat. activated by brief electric shocks applied to the contralateral optic nerve. yields two anatomical situations in which the effect upon the form of the recorded potential of branching and termination of fibers between electrodes may be investigated. In the dorsal nucleus of the lateral geniculate body the larger optic tract fibers divide dichotomously and terminate within one or another of the cell layers of the dorsal nucleus (Minkowski. 1920; O'Leary, 1940). In the *area striata* the optic radiation fibers divide dichotomously in the stria of Gennari, terminating in the layer of star cells and star pyramids (Ramon y Cajal, 1923; Lorente de Nó, 1938a; O'Leary, 1941) which is coextensive with it. It is probable that each of these situations provides more complications than can be visualized by any available histological method. but the appearance of the records coincides with certain of the theoretical expectations. In the case of the lateral geniculate body a diphasic plus-minus deflection is obtained when one recording electrode is placed along the course of the axons prior to their branching. or even in their vicinity, and a second beyond their terminations. The first electrode is negative to the second during the activity at the axon terminals. In the *area striata* (similar situations for the first and second electrodes) the first remains negative to the second even when the latter is placed in the region of the end-arborizations.

One feature of the above situation that should be emphasized is that a record can be obtained of activity at a point *between* the recording electrodes without having activity *at* either one of them. This is very important in considering the application of the data derived from records of activity in linear tracts to the cerebral cortex. Especially in the cortex where the major axis of orientation of neurons is vertical and many of these elements are of limited length, what happens between the electrodes may be as important as what happens in close proximity to them. A record of the activity between electrodes seems to be a function of the non-uniformity of the path, and may be contrasted with the case of two recording electrodes placed along an extensive linear tract.

When an impulse occupies a region *between* two such electrodes along a linear path. differences of potential exist along the tract from the active point which is negative to regions in either direction that are positive. These two differences of potential being oppositely directed will tend to affect each electrode equally, and no record will be obtained until the impulse approaches one of the electrodes; that is. no overall difference of potential is set up across the active region. and the potential disturbance is symmetrical along the axes of the elements. On the other hand, when

a non-uniformity exists between the electrodes such that the activity on the two sides of the transition zone has a different effective value, the potential differences between the active impulse as it arrives at the transition point and the inactive regions to either side of it are no longer equal. The resultant overall differences of potential between two inactive regions on either side of the active point may be recorded as a simple monophasic deflection, even though neither electrode is at the locus of activity.

The amplitude of such a record is higher the nearer the electrodes are to the active region and the larger the number of parallel elements involved, or the larger the cross-sectional area of the tract that contains them. This situation is exemplified in the *area striata* of the cat, which for this purpose is considered as the broadened end of a tract (the optic radiation). A large region of the *area striata* can be activated synchronously, as after stimulation of the contralateral optic nerve, or in the activity involved in the *alpha* rhythm. A large number of vertically oriented neuronal elements, each with a non-uniformity at a constant depth (the stria of Gennari), then acts like a polarized layer; and electrodes placed one above and one below this level record the differences of potential across it, practically independently of their distances from the active level. This is of significance in considering the *alpha* waves of the human electroencephalograms, which are of low amplitude as compared with those obtained from the exposed brain, not primarily because of the thickness of tissue between active cortex and the electrodes, but because both electrodes are on the same side of the surface of activity and the skull can thus serve as an effective shunt between them.

Transition from Dendrite to Axon

Beside the non-uniformities in synaptic centers which are due to the branching and termination of presynaptic axons, the other unique situation which affects the form of records of activity is the transition across the cell body from the dendrites to the origin of the axon. Does conduction of activity occur in dendrites and can it be detected if they are of sufficient length? Do the electrical records of activity from the bodies and dendrites differ from those of the axon and can the differences which exist in the single cells be deduced from knowledge of what occurs when layers of cells discharge simultaneously?[2] The answers to these and many other problems await the investigation of synaptic centers of varied configurations, as-

[2] Work in this developing field will be found in the following papers, which are perhaps too recent and too few to demand the removal of these question marks: Lorente de Nó, 1939, Renshaw, 1942, Bishop and O'Leary, 1942, O'Leary and Bishop, 1943

sessing the differences in the records of activity in terms of the differing morphological arrangements. Study of the synaptic activation of single large nerve cells such as the Mauthner cells in the medulla of fishes might provide the correct answers, but so far records in which the form of the potential can be studied have not been obtained from single cells.

The nearest approach that we now have upon which to base deductions as to the happenings in single cells during activity is the interpretation of records obtained from layers of cells simultaneously activated through their synaptic connections. The dorsal nucleus of the lateral geniculate body in the cat (O'Leary, 1940; Bishop and O'Leary, 1942) is a favorable situation for such deductions because the cell bodies are densely aggregated into layers and separated by relatively little neuropil. The middle of the nucleus forms approximately a plane structure consisting of three layers of cells; the presynaptic axons enter one surface of the plane (caudal and ventral) and the postsynaptic axons leave by the other (rostral and dorsal). There are no interneurons to complicate the discharge of the postsynaptic elements when they are fired by brief stimuli to the optic nerve. Another favorable anatomical situation facilitates the location of the exact level at which changes in the records are obtained as a *critical electrode* is gradually moved through the plane from the optic radiation to the optic tract. The cell layer which adjoins the optic radiation is activated from the contralateral eye, the intermediate cell layer from the homolateral eye. When stimuli are delivered periodically to the two optic nerves as the *critical electrode* moves deeper through the nucleus, changes appear in the form of the records which are attributable to the stimulation of one or the other optic nerve, recorded from different levels with respect to the layers of cells activated by each nerve

The following considerations are based on experiments in which *reference* electrodes are placed anteriorly in the caudate nucleus, medially at the midline of the thalamus, and caudally in the medial geniculate nucleus All of these points can be demonstrated to be isopotential in the electrical field about the activated dorsal nucleus. The *critical electrode* is so directed that it passes from the optic radiation rostral and dorsal to the middle region of the dorsal nucleus, through the cell layer and into the optic tract perpendicular to the radiation surface of the plane As it passes through the optic radiation the *critical* electrode records a positive postsynaptic spike against any one of the *reference* electrodes Caudal and ventral to the dorsal nucleus the same electrode records a nega-

tive postsynaptic deflection, and reversal from positive to negative takes place as the *critical* electrode enters the cell layers The reversal takes place somewhat deeper (by the thickness of one cell layer) when the homo- instead of the contralateral optic nerve is stimulated The reversal from positive to negative during a sequence of records may be taken to mean that there is a strongly negative region in the vicinity of the cell bodies and dendrites and a positive region in the vicinity of the active optic radiation arising from these cells So the paradox develops that the cells are negative to their axons, even as the latter are conducting "negative" impulses! This interpretation becomes more clear if the plane containing the cell bodies is visualized as a membrane so polarized during its

response that its rostral and dorsal (radiation) surface is positive to its caudal and ventral (optic tract) surface, and the potentials recorded at a distance from it are chiefly those of the field set up about it The potential field is so strong as to mask the specific but weaker potentials of the

tissues with which the critical electrode may be in immediate contact The polarization of the sheet of cells may be attributed to a longitudinal difference of potential along the axis of each element contained therein with relative negativity away from the radiation, relative positivity toward it

Therefore, the geniculate synaptic region seems to contain three structures in addition to pre- and postsynaptic linear axon tracts which contribute to an electrical record from electrodes placed in the region: the end-arborizations of presynaptic axons, the arborizations of postsynaptic dendrites, and the junctures between dendrites and postsynaptic axons through the cell bodies. From electrodes placed in the vicinity but not necessarily in contact with active tissue both pre- and postsynaptic activities are recorded on one aspect of the synaptic layer as positive waves, on the opposite aspect as negative waves. These deflections are of sufficient intensity to mask or obscure the record of activity of the axons leading to and from the synaptic region. Disregarding the detailed interpretation of form and polarity ultimately demanded, the point to be made here is that the record obtained from a synaptic region is predominantly *not* that assignable to nerve axons as found in peripheral trunks Records from the cortex may be expected to be even less assignable to axons as such, and the interpretation of cortical potentials may require an intricate consideration of distributions of potential about specific types of synaptic structures. Short of this the correlation between potential record and cortical architecture must remain a rough correlation only, and not a thorough explanation of the relation between structure and functioning

Interpretation of Cortical Potentials

There are two common motives in the investigation of cortical architecture One, the detection of cyto- and myeloarchitectonic fields which appear to have structural significance provides a histotopographical parcellation that has played a prominent role in stimulation and ablation studies of cortical function. However, the details of electrical recording from the cortex have not yet been perfected to the point where the Nissl method is generally useful in demonstrating the field boundaries of areas of specific response To be sure Kornmüller (1935) has described records of spontaneous activity which differ for different cytoarchitectonic fields, and O'Leary and Bishop (1938) have found that the limits of the visual cortex of the rabbit, as determined by mapping the responses to stimulation of the contralateral optic nerve, are practically coextensive with the cytoarchitectonic limits of the rabbit's visual cortex as determined by Rose (1931). Bremer and Dow (1939) mapped the cortical response to auditory stimuli

and found that the area concerned corresponded to a cytoarchitectonic area of uniform structure, which included the upper part of the sylvian gyrus, the posterior part of the anterior ectosylvian, and the middle ectosylvian gyrus. Bishop and O'Leary (unpublished observations) also found that when the visual cortex of the cat is mapped by responses to induced activity, it contains besides the *area striata* a significant overlap into an adjoining area of diverse cytoarchitectonic pattern. Likewise the records of optically induced activity that are obtained from the functionally homologous fields of rabbit and cat do not differ significantly in form of response, although the cat's visual cortex is much more highly differentiated. In the same animal (cat) records of induced activity from visual and sensorimotor fields (Heinbecker and Bartley, 1940) do not differ significantly in the form of the response. We may conclude, therefore, that the records of induced activity so far obtained do not exhibit obvious correlates with the usual anatomical criteria used to distinguish cytoarchitectonic fields, at least insofar as the form of the record is concerned.

The other motive actuating architectonic investigation has directed efforts toward reducing the complex structural relationships of large areas of cortex to a basic plan. Lorente de Nó (1938a) has long championed such a basic arrangement for the sensory cortex, and has implied that the path to enlightenment is the study of modifications of this basic plan which characterize the different cortical fields from mouse to man. If the electrophysiologist were able to construct the ideal cortex for testing the principles of electrical recording heretofore detailed, it would be even simpler than the basic plan developed by Lorente de Nó and would consist entirely of vertically elongated elements, each extending from the surface of the cortex to the basal white matter, and a means of activating them synchronously.

The pyramidal cells, or principal cortical neurons, are in fact such vertically elongated elements, the apical dendritic shafts arising from the cell bodies and extending to the surface layer and the axons proceeding to the basal white matter. The different depths in the cortex which the bodies of the pyramidal cells occupy varies the situations of the critical cell-axon junctures and diminishes or increases the lengths of the apical shafts. When we depart from such abstract concepts, innumerable differences other than size (compare granular pyramidal cells of layer IV with the giant Betz cells, layer V) lend individual character to the pyramidal cells whose bodies occupy different cortical depths and equivalent depths in different fields. The basal dendrites may be few or numerous and vary in degree of branching and in the direction in which they extend from the body. The large superficial pyramidal cells which occur at the border between layers III and IV in the human *area parastriata* have basal dendrites which drop verti-

cally through layer IV. The solitary Meynert pyramidal cells of layer V of the *area striata* have basal dendrites which are oriented horizontally. Within the same cytoarchitectonic field the basal dendrites may be directed horizontally in one situation (Meynert pyramidal cells, interhemispheric *area striata*, cat) or follow an obliquely descending course in another (the same cells, apex of the lateral gyrus). The latter variation in distribution of basal dendrites may be explained as due to differences in developmental dynamics related to the convolutional markings of the brain. Other variations, such as the loss of the apical shafts of star cells (layer IV, *area striata*), appear to have a deep underlying functional significance.

When the individual characteristics of all the pyramidal cells occupying different depths of the cortex in each field are summed together they lend to that field characteristic traits which are readily variable from preparation to preparation. These changing manifestations from field to field in the protoplasmic plexuses (cell bodies and basal dendrites) which occupy different depths of the cortex distinguish the results obtained by the Golgi method as applied to the study of cortical architecture.

To the interpreter of records of cortical activity the fact that the vertically descending axons of the pyramidal cells issue extensive intracortical arborizations is of utmost importance. Tedious investigation of fairly completely impregnated arborizations of single pyramidal axons shows that ascending collaterals which leave the shaft near the cell body may ascend obliquely to the plexiform layer This has been repeatedly verified for all cells except those of layer VI. The axonal shafts of these cells commence so far from the surface that negative findings are insignificant. Horizontal and ascending collaterals contribute to the axonal plexuses of the subjacent levels. It is exceptionally difficult to demonstrate the synaptic terminals of the horizontal and ascending collaterals of the pyramidal cell axons. Lorente de Nó (1933) has stated that there are two types of synapses in the cortex (collateral synapses, *boutons de passage*; terminal synapses, *boutons terminaux*). If these could be thoroughly investigated and systematized for the collaterals of the pyramidal cell axons, an important contribution to the study of cortical architecture would result. Numerous special variations in the distribution of the collaterals of pyramidal cell axons may be encountered Study of many preparations may reveal that the particular pyramidal cell that characterizes one or another cortical level may fail to issue horizontal collaterals to one or another of the subjacent levels. The axons of certain pyramidal cells also have developed the ascending collaterals at the expense of the axonal shaft, so that the shaft may be reduced to a tenuous filament or be entirely absent (pyramidal cells with arciform axons, *area striata*).

The other significant system of intracortical axonal arborizations arises from the short axon cells which are distributed throughout the cortex. Differences in shape of body, arrangements of dendrites, and habitation in the protoplasmic plexuses of one or another cortical level distinguish short axon cells whose axons also present special characters of ramification. Broadly speaking, short axon cells may be divided into two types, based upon the extent of the axonal ramifications. The *locally arborizing* types form closely meshed tangles of branches about the bodies of neighboring cells. The arborizations of *extensively arborizing* short axons may pervade several levels of the cortex. The most superficially situated short axon cells give axonal ramifications that extend downwards and horizontally. Those situated at an intermediate depth have arborizations that branch upwards, downwards, and horizontally. The deepest of these cells have ascending arborizations, and the writer includes in this category the cells with ascending axons described by previous investigators. Several typical short axon cells which occur in the visual cortex of the rabbit are illustrated in fig. 50. The arborizations of specific short axon cells which occur in special cortical fields distinguish the axonal plexuses found at different depths of the cortex. The other distinguishing feature of these plexuses is the orientation and density of distribution of the collaterals of the pyramidal cell axons.

Even a theoretically simple cortex must have a mode of activation. The activators enter the cortex through the basal white matter as projection, commissural, and association axons. Of these only the distribution of thalamocortical afferents is well known, and that knowledge is principally confined to the sensory cortical fields (Ramon y Cajal, 1911; Lorente de Nó, 1922 and 1938a). The geniculo-calcarine axons may be considered as an example. These enter the striate cortex obliquely and arborize at an intermediate depth which is coextensive with the layer containing *star cells and star pyramids* (IV). The writer has observed as many as fourteen orders of branching in the terminal distribution of a single well-impregnated axon. Callosal and commissural afferents probably have a more widespread vertical distribution. Their mode of arborization is well illustrated by Lorente de Nó (1938).

The way in which the elements of any cortex (pyramidal and short axon neurons and the arborizing axons of the afferent plexus) are interrelated to establish cortical circuits of activity is conjectural, and a topic to be treated with utmost conservatism until further facts are established. It would appear that the fundamental circuits are vertically disposed (Lorente de Nó, 1938a) and (for the sensory cortical fields) have their nodal points in the granular layer where the entering afferents articulate with the bodies and dendrites of the first cortical neurons. The extent to

which lesser circuits mingle with the basic ones and the combinations that are necessary to secure the synchronous activity of various combinations of pyramidal neurons in different cortical layers are entirely unknown. Lorente de Nó (1933) has provided excellent illustrations of the probable complexity of the synaptic connections of single cortical pyramidal cells
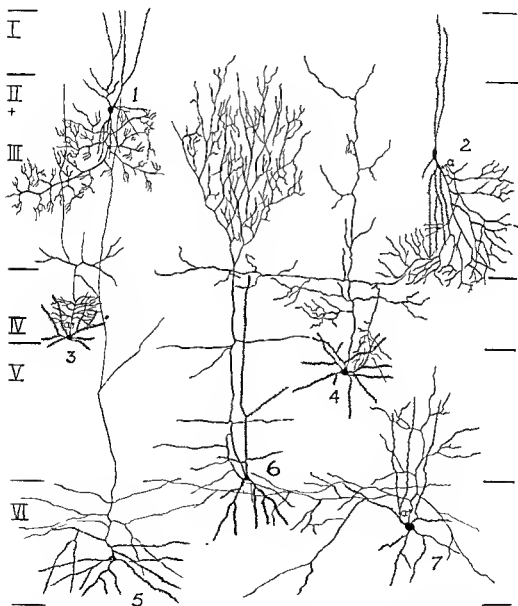
Fig 50 —Typical short axon cells observed in Golgi preparations of the visual cortex of the rabbit Cells *1, 2,* and *7* have axons of the *locally arborizing* variety Cells *3, 4, 5,* and *6* belong to the *extensively arborizing* type and have ascending axonal ramifications

The limits of the precentral cortex have been clearly established by Bonin in Chapter II. He has pointed out that the boundaries coincide closely with von Economo and Koskinas' *regio praerolandica*, and this is supported by Walker's (1938a and b) investigations upon thalamocortical connections (see also Chapter IV) and by the results of *physiological neuronography* as developed by Dusser de Barenne and McCulloch (Chapter VIII). Since the data relevant to this chapter have been acquired almost exclusively from the study of lower mammals, mention will be restricted to the significant problems of the primate precentral cortex which have a bearing upon correlations between electrical records and architectonics.

The agranularity of the precentral cortex has received significant mention in all related cytoarchitectonic studies. If accepted interpretations based upon knowledge of the sensory cortical fields were directly transferred to the precentral cortex, the paucity of granules in the latter might lead to the inference that an axonal plexus composed of arborizing thalamic afferents is absent. However, Ramón y Cajal (1911) gives a stratification of the precentral cortex which is not unlike that used by the modern school of investigators, and illustrates (fig. 406) a rich arborization of corticipetal fibers in a horizontal stratum corresponding roughly to the layer of medium-sized superficial pyramids. That this zone is not far beneath the surface of the cortex is evident from his figure 408, which is an illustration of the same arborizing afferents in the motor cortex of the cat. If the plexus thus formed represents the terminus of the thalamocortical radiation from the lateroventral thalamic nucleus (Walker, 1938a), we have in the precentral cortex a unique case of thalamic afferents terminating elsewhere than in the granular layer (IV). The other alternative, that this dense plexus is formed by arborizing commissural or association axons, is not a likely one.

Although specific attempts to relate the architectonics of the precentral cortex of the primate to the form of electrical records of induced activity have not been made, this cortex approaches the ideal one for the solution of related problems. The feasibility of such studies is evident from the success of Morison and Dempsey (1942) in recording localized responses from the cortex of the cat following stimulation in the thalamus. The probable direct articulation of the arborizing axons with cortical neurons of the classical pyramidal type (layer of medium-sized superficial pyramids) would appear to establish these cells as the nodal points of the basic activity circuits. The absence of a dense layer of cells of granule dimensions and the occurrence of the extraordinarily large cells of Betz are other characteristics of outstanding value. However, as a prelude to such an
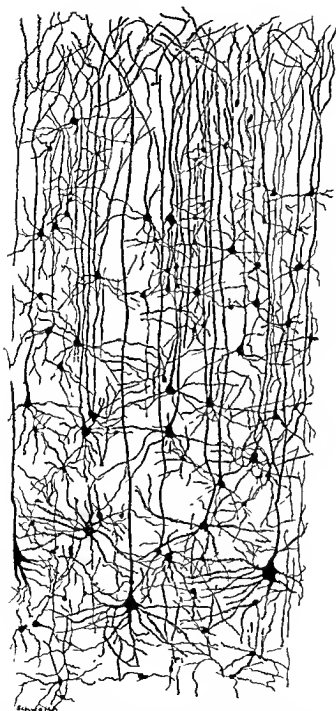
Fig. 51—Freehand sketch from a Golgi-Cox preparation of the precentral cortex (area 4 Brodmann) of *Macacus rhesus*. All extraneous impregnation, such as of the walls of blood vessels, has been eliminated. Area drawn situated in the rostral wall of the central sulcus. Three giant cells of Betz are shown.

investigation it will be necessary to make a systematic survey of the distributions of short axon arborizations and collaterals of pyramidal cell axons. The reader is referred to fig. 51 which is a freehand sketch of a small area of the macaque motor cortex made from a Golgi Cox preparation. . .

In summary of the essential anatomical characters of the cortex from the viewpoint of interpreting electrical records are: (1) The vertically oriented elements, which extend from the surface 'to the basal white matter, each consist of a pyramidal cell body, an ascending dendritic shaft, and a descending axon. Unique appearances of the pyramidal cells belonging to different cortical levels and to equivalent levels in different areas impart distinguishing features to the protoplasmic plexuses of the different cortical fields. (2) The chief intracortical connections are established through the collateral arborizations of the axons of pyramidal cells and the variety of short axon arborizations which occur at different levels of the cortex. (3) In the sensory cortical fields the cortex is primarily activated through entering afferents which arborize at a level of the cortex corresponding to the granule layer (IV); in the precentral cortex the apparently but not necessarily equivalent afferent plexus arborizes at a more superficial level, probably articulating directly with superficial pyramids of medium size. (4) The activation of the whole cortex would appear to proceed through intracortical circuits arising from cells situated within the confines of the plexus of arborizing afferents. The arrangement of all contained elements is such that adequate records of cortical activity can only be expected from an intact cortex containing *all* of the various vertically disposed elements.

Interpretation of Records of Cortical Activity

The integers for the interpretation of records of cortical activity are the ways in which neurons are grouped, summed, and recorded. The first two are not controllable, nor are they basically understood. By experimental variations in the positions of the recording electrodes most of the information acquired concerning the relations of cortical potentials to architectonics has been obtained. Thus far these acquisitions of knowledge apply only to the simplest relationships, but even these are of the utmost importance, since they direct attention to the course that future investigations must take.

"Spontaneous" fluctuations of different frequencies (the *alpha* and other rhythms) are the most universally studied patterns of cortical activity. The fluctuations recorded as "spontaneous" activity may in one case represent the mutual facilitation of parallel elements and in another completely random activity. It has been suggested previously (p. 93) that the theoretical limit of the latter is a smooth base line that indicates
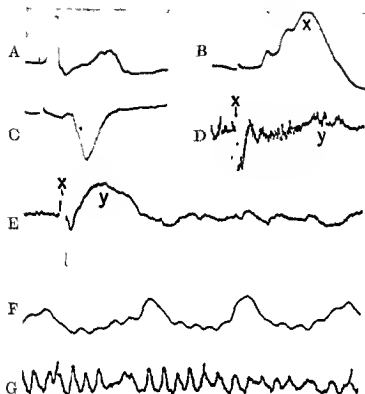
Fig 52—Analytical development of the electroencephalogram

A Splanchnic nerve of the bullfrog stimulated by a single shock The first wave is a record of radiation axons The following irregular elevation is that of groups of fine non-myelinated fibers The separation of the waves is due to differences of conduction rate between different groups of fibers

B Response of the optic cortex of the cat following a single shock to the optic nerve The first wave is the record of radiation axons, the second of the first cortical neuron, etc In contrast to *A*, the separation of waves is due to time occupied in the passage of the impulses across synapses The first interval between the shock artifact and the radiation wave, includes conduction time in the tract, synapse time across the lateral geniculate nucleus and the cortex a total of about two one-thousandths of a second

C A record of the response of cat optic radiation fibers alone, recorded below the cortex The duration of the wave is about one-thousandth second, comparable to the first spike of *A*, which is on a shorter time line than *C*

D Cortical response as in *B*, but on slower time line The whole record of *B* is condensed into the first upward deflection marked *x*, the following downward deflection is off the record in *B* Each minor jiggle in *D*, is actually of the duration of the wave in *C*, or of each successive wave in *B*

E Record similar to *D*, but slower time and amplifier of oscillographic recorder damped down so that it does not follow the fast minor deflection in *D* Following the first response complex, *x*, is an *alpha* wave, *y*, resulting from the stimulus The interval between *x* and *y* is about one-sixth second

F Spontaneous *alpha* and *beta* waves, cat, amplifier still more damped than in *E*

G Still further damping and time line further slowed, *alpha* waves prominent, beta waves nearly eliminated The three vertical deflections are 12 seconds apart The record as presented is comparable to that recorded on an ink-writing encephalograph The actual response of the cortex involved, however, such details as are more apparent in the previous records

no activity at all. The system of recording is another important factor in the interpretation of "spontaneous" records, since only with inertialess systems are all the complications of the records preserved. When these complications are removed from the records, as in tracings from slow ink-writing devices, attempts to assign relationships between activity and architectonics are rendered impossible. Figure 52 traces the analytical development of the electroencephalogram from the simple record of peripheral nerve responses to the conventional record of cortical activity. From examination of this figure it is apparent how much of the detail of the cortical response is missing from records of "spontaneous" activity.

Another factor which entails consideration in interpreting "spontaneous" potentials led from the cerebral cortex is that the frequency of recurrence of characteristic fluctuations is not determined wholly within the cortex. For example, if the optic radiation is cut, the *alpha* rhythm (5–6 per second) recorded from the optic cortex of the rabbit under light Dial anesthesia is replaced by slow waves having a frequency of less than one per second. Other evidence indicates that activity over callosal axons similarly modifies the frequency of cortical waves.

Cortical potentials induced by stimulation of peripheral nerves have decided advantages in studying the manifestations of cortical activity. These were mentioned when the responses of the lateral geniculate nucleus were discussed and are further emphasized by reference to fig. 52. The experience of the author with this line of investigation has been confined to the visual cortex activated through the contralateral optic nerve. The recording electrodes may be so arranged as to subtend the entire thickness of the cortex or any reasonable fraction thereof. Consequently, in the same experiment it is possible to study the individual records of this response as obtained from electrodes which subtend different horizontal levels of the cortex, comparing them with similar records of the "spontaneous" *alpha* rhythm. The results of such comparisons provide the basis for conjecture as to the elements in the cortex responsible for "spontaneous" and induced activity.

As recorded from paired needle electrodes placed one at the surface and one at the base of the visual cortex, the response to stimulation of the optic nerve consists of three series of events. The first is a swift succession of short waves having the dimensions of axon spikes. By comparison of cortical records with those obtained from the optic radiation and lateral geniculate nucleus, it is evident that the first of these signalizes the response of the axons of the optic radiation. The second spike is confined to the cortex and presumably represents the spread of the impulse to the first cortical neurons, which by inference from anatomical data should be situated in the granule layer (IV). The third spike of this series bears a definite time

relation to a spike which occurs in records of the superior colliculus (Bishop and O'Leary, 1938), and we have inferred that it is representative of corticifugal axons discharging to that nucleus.

The second series of events consists of a mono-, di-, or triphasic wave, each of the first two phases being 5 to 10 Msec. in duration. The first phase of this series is surface positive and rises from the base line with the second spike of the preceding series. It does not represent the responses of the same elements as occasion the second phase, for under certain conditions of recording, the second, or surface negative phase, may drop out completely leaving the first unaffected. Furthermore, strychninization of the cortical surface, which may slightly increase the amplitude of the first phase, greatly exaggerates the second one and may delay its occurrence until an appreciable interval after the termination of the first. The third, or surface positive, phase of this series is inconstant in occurrence, exaggerated by strychninization as is the second, and may be occasioned by the discharge of the same elements as are responsible for the second phase.

The third series of waves are still slower and have the dimensions of "spontaneous" *alpha* waves. While a train of two or more of them frequently follows the stimulus in the rabbit, they are not constantly observed in experiments upon the cat. Their occurrence in that animal depends upon the depth of anesthesia and possibly upon other unknown factors. For example, it has not been determined whether they will occur in response to electrical stimulation of the optic radiation when that tract is severed from its connection with the lateral geniculate nucleus. This third series of induced potentials, apparently simply an alpha rhythm started by the stimulus, certainly occupies different elements in the cortex than the specific response to afferent stimulation which precedes it. Further differential procedures indicate that there exist two distinguishable but overlying systems of neurons in the cortex generally, although these two systems are complexly interconnected. They have not been differentiated histologically. It is not known to what extent the afferent-response or projection system is represented in the usual electroencephalogram, but it must certainly be activated in epileptiform convulsions, as it is in those induced by strychnine.

When different fractions of the cortical thickness are recorded and compared, the most significant fact determined is that the first complex (consisting of surface positive short spikes and the first surface positive phase of the second series) is recorded predominantly from the upper three layers of the cortex (Bishop, unpublished observations). It will be recalled that the surface positive phase rises from the base line coincident with the appearance of the second brief spike of the first series, which we believe signalizes the activation of the first cortical neuron. If this surface positive

phase consisted of innumerable summed axon responses it might be produced in the dense axonal plexus of non-myelinated axons that occupies the interstices between the bodies of the superficial pyramids. A more interesting but less conventional speculation is based upon the demonstration that in the lateral geniculate nucleus, during activity the cell body is predominantly negative as compared even with its active axon (p. 98). Since all of the critical cell-axon junctures of superficial pyramidal cells occur within that layer, and below this these cells are represented only by their axonal shafts and collateral arborizations, such a surface positive phase might result from predominant activity in cells and dendrites as compared with axons. Thus, though a definite relation is demonstrable between the first phase of the second series and the layer of superficial pyramidal cells, the choice between alternative explanations must await more thorough investigation.

Curtis (1940) applied single electrical shocks to the cortex of one hemisphere in cats and monkeys and recorded the evoked potentials from the other. The waves were diphasic and were largest when stimulating and recording electrodes were placed on symmetrically situated points in the two hemispheres. The responses were abolished after section of the corpus callosum. Each consisted of an initial surface positive component lasting 15 Msec. and a following surface negative one lasting about 75 Msec Convulsant drugs slightly increased the surface positive component, and greatly increased the surface negative one By subtending various cortical depths with microelectrodes, Curtis obtained results suggesting that ascending (callosal) axons give rise to the surface positive component, descending interuncial fibers passing to the deeper layers give rise to the surface negative component. The similarity of his results to those reported above is of particular interest in pointing out that the general form of the cortical record of induced activity may be the same, even though the cortex is activated through its thalamic afferents in one case, and its callosal afferents in another.

Study of the "spontaneous" *alpha* waves by electrodes which fractionate the cortex into horizontal levels yields results different from those obtained through the study of induced activity. The total amplitude of the *alpha* waves is obtained when one electrode is situated at the surface and another at or near the basal white matter. Any fraction of the total cortical thickness yields a proportionate fraction of the amplitude of the total response. This suggests either that cellular elements which give rise to the *alpha* waves are situated deep in the cortex and have apical shafts that extend to the surface or that they are evenly distributed throughout (pyramidal cells with bodies situated in all layers). The alternative to this explanation, based upon the level of occurrence of the critical cell-axon

junctures, is that the *alpha* waves represent summed axon responses arising from the plexuses of axons that lie in the interstices between the cell bodies When speculation is left entirely aside, it is evident that the *alpha* mechanism is a property of the whole cortical thickness and not of a fraction thereof Adrian and Moruzzi (1939) appear to hold a similar view, that elements of both superficial and deep layers are responsible for waves of *alpha* frequency that they recorded from the motor cortex of the cat

Renshaw, Forbes, and Morison (1940) have applied the technique of recording with microelectrodes to the study of the activity of the hippocampus and lateral gyrus (cat). The technique of recording single units from closely spaced microelectrodes is the converse of the one emphasized in this chapter, which is concerned with attempts to deduce the activity of single units from records of tissue masses. The recording of single units offers unlimited possibilities, particularly if it is used in situations where nerve cells are uniquely set apart in their environment, as the Betz cells of the motor cortex are by their size Just as cytoarchitectonic parcellation and cortical records of induced activity are analogous in that they deal with *areas* rather than with single cells, so the perfection of single unit recording may provide the electrophysiologist with a "Golgi" method.

The accumulation of data and speculation thereupon can continue, though direct proof is wanting concerning what constitutes the circuits of activity. The latter problem is the anatomical equivalent of the functional puzzle as to how grouping and summation occurs in cortical neurons. Together the anatomical and functional unknowns are a part of the much larger problem of how interchange between the essential elements of different circuits brings about the kaleidoscopic shifts in pattern that must form the basis of mental activity.

Summary

In the first sections of this chapter the simplest electrical records obtainable from the CNS, those from linear tracts, are analyzed by reference to the conditions that determine the form of the action potential in isolated peripheral nerves The observations illuminate the pitfalls that may trap those who attempt to relate cytoarchitecture to electrical activity Series of records obtained from a *critical* electrode thrust through the cell layers of the lateral geniculate nucleus (recorded against one of several reference electrodes) are used to demonstrate how the records from simple linear tracts may be applied to the investigation of synaptic centers having a relatively well-known anatomical structure Finally the essential anatomical facts about the cerebral cortex which may be significant in the interpretation of electrical records are presented, to show how correlates between anatomical and functional data can be obtained.

Chapter IV

AFFERENT CONNECTIONS

A. Earl Walker, M.D.

Professor of Neurological Surgery
The Johns Hopkins University
and
Neurosurgeon-in-Chief
The Johns Hopkins Hospital

OUTLINE OF CHAPTER IV

Afferent Connections

ABBREVIATIONS USED IN FIGURES 53-62

AV	Nucleus anteroventralis	NC	Nucleus caudatus
C	Sulcus centralis	NR	Nucleus ruber
CC	Corpus callosum	OC	Chiasma nervorum opticorum
CI	Capsula interna	OT	Tractus opticus
CL	Corpus Luysii	PE	Sulcus parietooccipitalis externus
CM	Nucleus centrum medianum	R	Nucleus reticularis
CMa	Corpus mammillare	S	Corpus subthalamicum
CP	Pes penduncli	SC	Sulcus callomarginalis
CS	Sulcus centralis	SS	Sulcus sylvii
GC	Gyrus cinguli	SN	Substantia nigra
GP	Globus pallidus	VA	Nucleus ventralis anterior
IC	Capsula interna	VdA	Fasciculus thalamomammillaris
LD	Nucleus lateralis dorsalis	VL	Nucleus ventralis lateralis
LG	Corpus geniculatum laterale	VP	Nucleus ventralis posterior
M	Corpus mammillare	VPL	Nucleus ventralis posterolateralis
MD	Nucleus medialis dorsalis	VPM	Nucleus ventralis posteromedialis
MG	Corpus geniculatum mediale		

AFFERENT CONNECTIONS

THE FIBERS entering the precentral motor cortex originate predominantly from adjacent areas of cerebral cortex or from the thalamus. Exact data on these fiber pathways are not well known, due to the inadequacies of the experimental methods used in research on nerve tracts. It is perhaps advisable to discuss some of these techniques, their limitations and fallacies. Excluding gross neuroanatomy, three main methods have been used to study the afferent connections of the cerebral cortex; the Marchi, retrograde cell degeneration, and strychninization methods. As might be expected, these three techniques do not give similar results.

Marchi Method—Introduced by Marchi in 1885, this capricious technique has been the most widely used method in tracing nervous pathways. It depends upon the fact that products of degeneration of myelin sheaths can be stained specifically after mordanting with a chromic salt. The method does not demonstrate unmyelinated fibers, and frequently, finely myelinated fibers cannot be detected. The method has the disadvantage of being so sensitive that it must be carried out with the greatest care to avoid false degeneration ("pseudo-Marchi"). This is evidenced by the fact that almost every investigator has some special trick which he uses to avoid the undesirable precipitation. But even with special precautions there is usually a certain amount of "stippling" in the heavily myelinated tracts; for this reason caution must be exercised in interpreting what is seen in these preparations (C and O. Vogt, 1902).

Nissl Method—In 1892 Nissl demonstrated that certain changes occurred within the neuron when its axon was cut. Such retrograde cell changes have been extensively used in the study of the thalamocortical connections. Because most of the thalamic cells whose axons are damaged by a cortical lesion quickly degenerate and are replaced by glia, this method is quite satisfactory. However, if only a small percentage of cells are degenerated, especially if the lesion is old, it is difficult to detect the decrease in neurons and the mild gliosis. Hence the method cannot be considered very sensitive. Moreover, when applied to neurons other than the thalamus further difficulties are encountered, for all damaged neurons do not undergo retrograde cell changes at the same time, and some apparently show little alteration from normal (Walker, 1938a).

Strychninization Method—This method, developed by Dusser de Barenne and his associates, has been used extensively to study the connections within the brain (see Chapter VIII). By its use, the projection of a system

of fibers and their polarity can be determined within a few minutes. The obvious objection to the method, that little is known of its mechanism, becomes less important as more and more data are accumulated. Like the Marchi technique, its extreme sensitivity gives maximal results.

Cortical Afferent Connections

A more detailed description of the intercortical connections is presented by McCulloch (Chapter VIII), so that only those observations demonstrated by the Marchi technique will be discussed here. The entire investigation has been made on the macaque monkey, there being no pertinent data on the chimpanzee or man.

Area 4—The motor area has been found to receive an extensive afferent cortical radiation both from the same and opposite cerebral hemisphere. Mettler (1935a, b, c; 1935-1936) states that fibers enter it from areas 1, 2, 3, 5, 7, 8, 9, 10, 17, 21, 22, and even from other parts of area 4. There is no evidence from Mettler's studies that these intercortical connections respect the functional somatotopic boundaries. Thus the face, arm, and leg divisions of area 4 are interconnected, and the postcentral cortex of one subdivision sends fibers to all three subdivisions of the precentral gyrus. Mettler's claim that area 17 sends fibers to the motor area has not received confirmation from a number of investigators (Biemond, 1930; Le Gros Clark, 1941), nor have I been able to confirm it. Biemond (1930) does describe fibers passing from the upper part of the parietal lobe to the inferior part of the precentral gyrus.

Area 6—Mettler (1935a, b, c; 1935-1936) found fibers entering the upper part of area 6 from the adjacent areas and from distant zones. Areas 1, 2, 3, 5, 17, 21, and 22 all sent fibers to area 6. "U" fibers can be seen in myelin stained sections to enter area 6 from area 4. Area 44 (area 6b) according to Mettler (1935a, b, c; 1935-1936) receives fibers from areas 10 and 22.

Other Cortical Fields—Little can be said about the cortical connections to the other cytoarchitectural areas of the precentral motor cortex. In many cases these areas are small, and their boundaries indistinct, so that in Marchi preparations in which cytoarchitectural structure is poorly shown these areas cannot be recognized.

A carefully planned anatomical study of the intercortical connections, with particular reference to cytoarchitectural fields, is greatly needed to clarify many points.

Cortex of the Opposite Hemisphere—Mettler (1936) found that if a point *A* is associated with a number of other points in the same hemi-

sphere, then it has callosal connections to homologous points including A' on the opposite hemisphere. This principle has been confirmed at least in part by Curtis (1940) using evoked potentials. He found that a single electrical shock applied to the pial surface of one hemisphere will usually evoke a potential at one or more points in the opposite hemisphere. The most readily detected potentials occur at the symmetrically situated point on the opposite hemisphere. Thus all points of the precentral motor cortex presumably receive afferent fibers through the corpus callosum from symmetrically situated cortical areas. Other connections through the corpus callosum from areas 1, 4, 5, 6, and 7 to the precentral motor cortex were demonstrated by this method.

Thalamic Projection

Before considering the projection to the individual cytoarchitectural areas of the cerebral cortex it may be well to discuss some general principles of thalamic projection. It has been conclusively shown in the macaque monkey that the anterior half of the lateral nuclear mass projects to the motor and premotor cortex. This portion of the thalamus has been termed the nucleus ventralis lateralis (Walker, 1937). Histologically it has a fairly uniform structure, although it is possible to subdivide it on a morphological basis into smaller units (see Vogt's, 1909, and Grünthal's, 1934, divisions). There appears to be no physiological rationale at the present time for such a further classification; in fact, finer divisions are only confusing.

Polyak (1932) has emphasized the fact that the thalamic radiation appears to be in fans oriented anteroposteriorly. The anterior fan projects to the precentral subsector or the motor and premotor cortex, the intermediate fan to the cortex along the central sulcus and the posterior fan to the parietal lobe. That such an arrangement holds for man has not been clearly demonstrated. Wenderowicz (1915) has shown a projection from the thalamus to the precentral convolution in man using the Marchi technique, but the projection in this case did not extend farther than the precentral sulcus. Whether this was due to the locus of the lesion, which does not seem likely, to the caprices of the Marchi technique, or to the fact that the fibers passing through the more anterior portion of the internal capsule are finely myelinated, cannot be definitely stated. In Probst's case (1906), however, sparse Marchi degeneration was followed to the posterior portions of the frontal convolutions as well as to the precentral gyrus. Although the number of degenerated fibers decreased anteriorly, there appeared to be a fairly even distribution of the fibers to the precentral and posterior parts of the frontal gyri. In the chimpanzee and man there does seem to be some evi-

dence to support the hypothesis of fan-like radiations to the precentral motor cortex. In other words, the more anterior portions of the thalamus send their fibers to the more anterior portion of the precentral motor cortex. Papez (1940a) concluded from his studies that the termination of the dentato-rubro-thalamic fibers in the ventrolateral nucleus lies posteriorly and laterally to the termination of the lenticulothalamic fibers, and that the projection to the precentral motor cortex from the ventrolateral nucleus of the thalamus retains this same anteroposterior orientation; i.e., the cerebellar impulses are relayed primarily to area 4, whereas the impulses from the lenticular nucleus are transmitted predominantly to area 6. Thus Papez's observations in the human brain further confirm Polyak's observations that the thalamocortical fibers are arranged in a series of fans oriented anteroposteriorly. The following case illustrates the thalamic connections to the precentral motor cortex.

CASE 1

On March 6, 1939, a twenty-four year old man (LP, Unit No 216063) was referred to the University of Chicago Clinics by Dr M Koenig, of Hammond, Indiana Since

the age of twelve he had suffered from involuntary movements of the extremities, trunk, and head, which gradually increased in severity and extent At the time of ad-
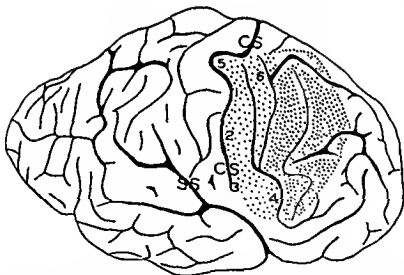
FIG 53 (Case 1)—Sketch of the right cerebral hemisphere showing the extent of the extirpation (dense stippling) and the subpial dissection of the cortex (sparse stippling) From the points marked the following responses were obtained upon electrical stimulation (1) flexion of the fingers of the left hand, (2) retraction of the left corner of the mouth, (3) closure of the mouth, (4) movement of throat musculature; (5) flexion of the left elbow, (6) elevation of the left shoulder

mission he presented the clinical picture of dystonia musculorum deformans.

In two stages the face and arm portions of areas 4 and 6 were removed from the right hemisphere. Three months later the face and arm fields of areas 4 and 6 were removed from the left cerebral hemisphere. After each of these procedures a temporary improvement was noted in the involuntary movements. He died thirty-nine days after the last operation.

Gross Description of the Brain

On the right side the dura mater under the bone flap was thickened and on the left side covered by a thin stratum of dark, coagulated blood. The cerebral hemispheres were symmetrical. At the frontal poles the sulci were widened and the convolutions slightly atrophic. The parietal, occipital, and temporal lobes were normal. The cerebellum was well developed. At the base of the brain the vessels were thin-walled and free from atheromatous plaques. The circle of Willis was intact anatomically.

In the right frontal lobe was a large cortical extirpation covered with a thick, opaque membrane, which extended from the Sylvian fissure to within 1.5 cm of the midline. It reached in front of the central sulcus for a distance of 6 cm. superiorly and 4 cm inferiorly. Posteriorly the base of the ablation was only 2 to 3 mm below the surface of the cortex, but anteriorly the crater was depressed 10 mm (fig. 53).

The extirpation on the left side did not quite reach the Sylvian fissure and extended superiorly to within 2.6 cm of the midline. It reached 4 cm. anterior to the central sulcus superiorly, but at its inferior extremity it was only 2 cm. from that sulcus. The crater was much deeper anteriorly than posteriorly (fig. 54).

Complete serial sections were made of the frontal lobes and the basal ganglia.

Microscopic Description of the Right Cerebral Hemisphere

Cortex.—The most medial part of the lesion lay in the superior frontal gyrus and was bounded by area 6 cortex. The lesion extended posteriorly to the central sulcus, but a considerable amount of area 4 cortex was still present on the anterior wall of this sulcus. On the walls and trough of the precentral sulcus, cortex of area 6 remained. The
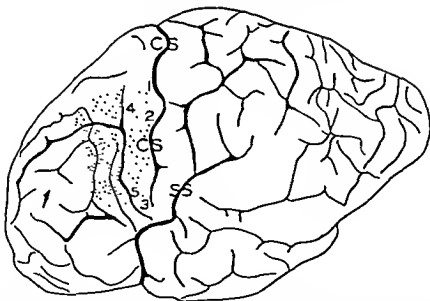
Fig. 54 (Case 1).—Sketch of the left cerebral hemisphere showing the extent of the extirpation (dense stippling) and the subpial dissection of the cortex (sparse stippling). From the points numbered, the following responses were obtained upon electrical excitation: (1) extension of the right wrist and fingers; (2) retraction of the right angle of the mouth; (3) elevation of the larynx; (4) closure of the eyelids; (5) elevation of the lower jaw.

anterior margin of the upper part of the ablation was area 6 At the level of the inferior frontal sulcus the rostral border of the lesion was bounded by granular cortex Along the central sulcus at this level most of area 4 was ablated In the lower part of the lesion, the anterior border was area 9 cortex, but the inferior margin was bounded by area 6 to the tip of the central sulcus

Thalamus—Although pathological alterations in neurons were present in practically every part of the brain the retrograde cell degeneration was easily distinguishable These changes in the thalamus were con-

fined to the nuclei ventralis lateralis and medialis dorsalis The degeneration began near the caudal extremity of the nucleus ventralis anterior It rapidly became much more extensive, occupying almost the whole of the nucleus ventralis lateralis at the level of the subthalamic body In the caudal half of the nucleus ventralis lateralis the degeneration was less extensive and largely confined to the medial part of the nucleus The degeneration terminated above the rostral portion of the nucleus centrum medianum At almost its rostral tip the nucleus medialis dorsalis exhibited a zone of
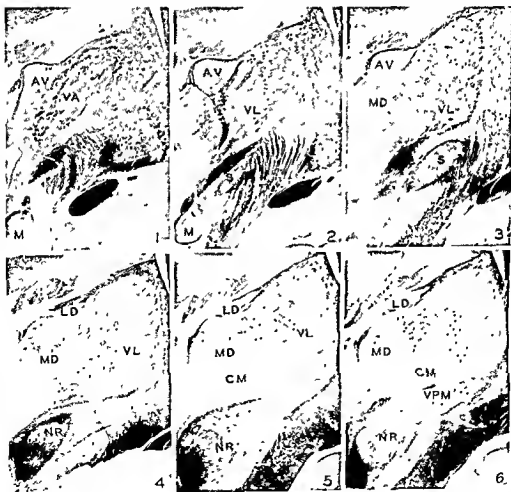
Fig. 55 (Cise 1)—Photomicrographs of six representative serial sections of the right thalamus with the site of the retrograde cell degeneration indicated by stippling (Smith-Quigley method for myelin)
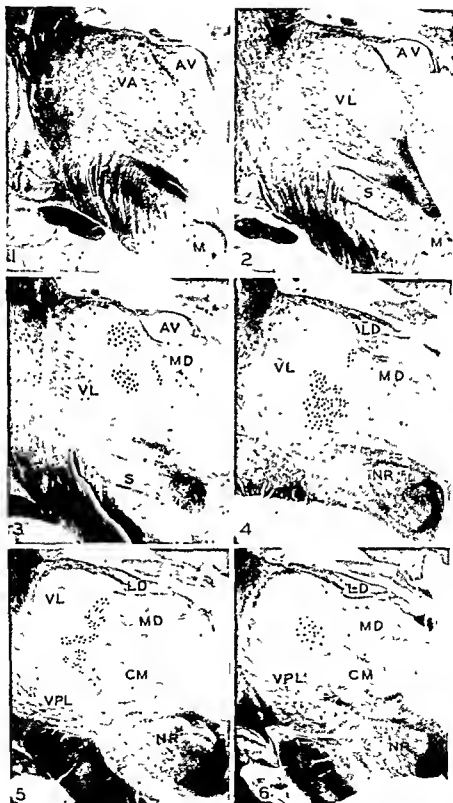
Fig. 56 (Case 1)—Photomicrographs of six representative serial sections of the left thalamus, with the site of retrograde cell degeneration indicated by stippling (Smith-Quigley method for myelin)

cellular degeneration along its lateral margin While maintaining relatively the same position, the degeneration became slightly larger in more caudal sections but terminated in the posterior third of the nucleus (fig 55)

Microscopic Examination of the Left Cerebral Hemisphere

Cortex—An examination of serial sections of the left frontal lobe revealed that the removal of the precentral convolution was incomplete A considerable portion of area 4 lying along the anterior wall of the central sulcus remained undamaged Cortex remaining on the walls and trough of the inferior precentral sulcus was cytoarchitecturally area 6 The margins of the ablations appeared to be lined with cortex of area 6 except at the middle frontal gyrus where granular frontal cortex abutted the extirpation Inferiorly the ablation extended to the margin of area 44 but was bounded by area

6, except on the margin of the central sulcus where area 4 cortex was present Thus a part of area 4, 4a, a considerable part of area 6, and a small portion of area 9 were involved by the extirpation (fig 54)

Thalamus—The degeneration in the thalamus was clear. It took the form of patches of gliosis in the nuclei ventralis lateralis and medialis dorsalis The degeneration began near the caudal extremity of the nucleus ventralis anterior as small discrete areas of gliosis in the dorsal and medial portions of the nucleus ventralis lateralis At approximately the same level a small zone of cellular degeneration was present in the paralamellar part of the nucleus medialis dorsalis in a few sections The degeneration in the nucleus ventralis lateralis was extensive but patchy and was confined to the medial half of the nucleus It extended caudally slightly posterior to the rostral tip of the nucleus centrum medianum (fig 56)

It is evident from the findings in this case that the thalamic projection to the arm and face fields of areas 4 and 6 of the cerebral cortex originates from the nucleus ventralis lateralis and mainly from its medial moiety. The degeneration within the nucleus medialis dorsalis in this case is the result of damage to the granular prefrontal cortex (Walker, 1938b).

There is also a somatotopic organization within the thalamic radiation to the precentral convolutions In the macaque monkey this can be easily demonstrated by examining the degenerations following lesions of the cerebral cortex in the leg, arm, and face fields. These degenerations occur in the lateral, intermediate, and medial portions of the ventrolateral nucleus of the thalamus respectively. In the chimpanzee it also has been shown that such an arrangement is present, although the evidence in the chimpanzee is perhaps not so conclusive as in the macaque monkey. Although the evidence for this arrangement in man is not too satisfactory there are certain reports (Fukuda, 1919, cases 1 and 8; case 1 of this chapter) that seem to suggest such a somatotopic organization of the thalamic projection to the cerebral cortex. That this projection adheres to the precise boundaries that Dusser de Barenne and McCulloch (1938a) have found, using the method of strychninization, cannot be stated at this time. Certainly the mediolateral orientation is much more precise than the anteroposterior arrangement of the thalamic projection in which there is a great deal of overlapping. In fact, using the Marchi technique, some of the earlier investigators (Sachs, 1909, and more recently Crouch, 1940) have stated that the projection to the precentral motor cortex occurs from both

the ventrolateral and the ventroposterior (or ventroposterolateral and -medial) nuclei of the thalamus. These investigators do not believe that there is the clear-cut differentiation of the thalamic projection to the cerebral cortex which the use of the method of retrograde cell degeneration would lead one to suppose It is probable that Crouch (1940) is correct in his contention that there is a projection from the posterior ventral nucleus of the thalamus to the precentral motor cortex, which cannot be demonstrated by the retrograde cell degeneration methods, due to the fact that the projection is much scantier than that from the ventrolateral nucleus. Such an afferent connection would be in accord with the findings of Dusser de Barenne and Sager (1937) who, by strychninization of any portion of the ventral nucleus of the thalamus, found connections to both pre- and postcentral convolutions. This dual thalamic projection, however, does not nullify in any way the general organization of the thalamic projection to the cerebral cortex. It merely indicates the presence of complex pathways by which the precentral motor cortex is maintained in contact with the various modalities of sensation.

Thalamic Connections to Cytoarchitectural Areas

The precise arrangement of the thalamic connections to the individual areas of the precentral motor cortex is fairly well known in the monkey and chimpanzee, but for man there is little data.

Area 4—In the lower primates area 4 comprises a relatively large proportion of the precentral motor cortex, but in the higher primates area 6 is predominant (see Chapter 11) Accordingly the relative size of the thalamic projections to these areas varies in the ascending primate scale. In the macaque monkey (Polyak, 1932; Walker 1938a) area 4 derives a rich supply of fibers from the anterior half of the lateral nuclear mass whereas area 6 receives only a few fibers. There does not appear to be a distinct locus in the nucleus ventralis lateralis from which the fibers to area 4 originate. In fact, after removal of the precentral convolution of this animal it is at times difficult to detect the retrograde cell degeneration, so diffuse is it in the nucleus ventralis lateralis. In general, however, it appears that area 6 receives most of its fibers from the dorsal and medial parts of the nucleus ventralis lateralis and area 44 from the ventral and medial part, the remainder of the nucleus sending fibers to area 4. In the chimpanzee the thalamic projection to area 6 is much greater than that to area 4. It is increased relatively more than that to area 4 in the monkey. As an illustration of this fact the degeneration in the brain of chimpanzee "Becky" may be compared with that of chimpanzee "Mussai" (Walker, 1938b).

CASE 2

The following operative procedures were performed on a female chimpanzee ("Becky")

March 22, 1934   Ablation of the left frontal association area

July 12, 1934   Ablation of the right frontal association area

December 2, 1936   Ablation of the left premotor area

March 12, 1937   Ablation of the right premotor area

For over four years until the time of sacrifice, June 17, 1938, the animal was studied psychologically by Dr Carlyle Jacobsen   As the two hemispheres are essentially the same, only the left will be described in detail.

Gross Description of the Left Cerebral Hemisphere

The cortex of the occipital and temporal lobes of this hemisphere appeared normal There were three clips along the inferior postcentral sulcus, and the cortex along the lips of this sulcus appeared to be lacerated to some extent   The frontal lobe anterior to the precentral gyrus was almost completely ablated (fig 57) Superiorly the margin of the ablation began along the midline 1 5 cm anterior to the central sulcus, passed laterally and paralleled the anterior lip of the central sulcus to within 1 1 cm of the Sylvian fissure, where it turned anteriorly to the inferior surface of the frontal lobe,
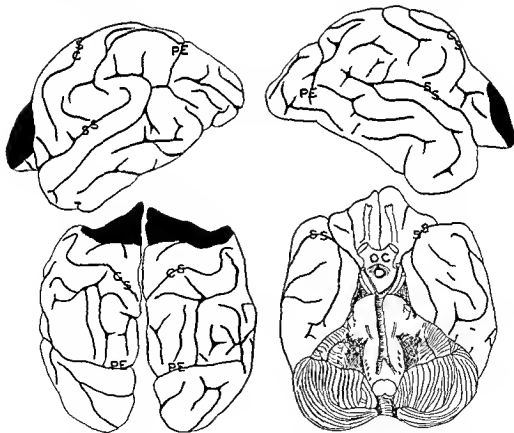
Fig 57 (Case 2) —Sketches of the brain of chimpanzee "Becky," to show the frontal extirpations
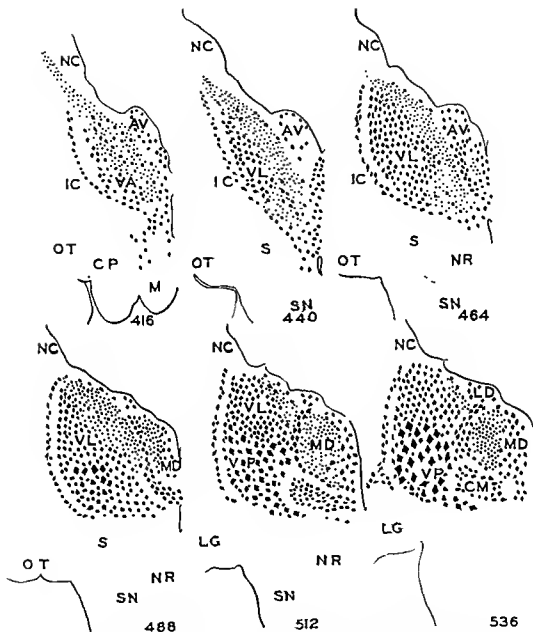
FIG. 58 (Case 2)—Sketches of representative serial sections of the thalamus with the site of retrograde cell degeneration indicated by round stippling. The angular stippling represents normal neurons.

passing 1 to 2 mm from the upper margin of the Sylvian fissure. It crossed the frontal lobe 1.5 cm anterior to the optic chiasm. Along the medial surface the lesion sloped to the dorsal aspect of the corpus callosum, 1 to 2 mm of cortex remaining above the

corpus callosum in the cingular gyrus. The denuded surface of the frontal lobe was covered by a thin arachnoid membrane, but the membrane did not cover the anterior horn of the lateral ventricle, in which the head of the caudate nucleus could be seen

Microscopic Examination of the Left Cerebral Hemisphere

The olfactory tracts seemed to be intact. The cortex of the gyrus rectus and inferior and medial surfaces of the hemisphere posterior to the anterior horn were undamaged. The lesion passed across the isocortex of the orbital surface and opened into the anterior horn of the lateral ventricle at its rostral extremity. The lesion had taken out a considerable portion of the lateral surface of the nucleus caudatus as far posteriorly as the oral extremity of the Sylvian fissure. The fibers of the rostrum of the corpus callosum were completely degenerated, and only a thin strip of cingular cortex lay above the corpus callosum anterior to the rostral portion of the thalamus. The opening in the lateral ventricle extended posteriorly to the level of the foramen of Munro. At the level of the rostral part of the Sylvian fissure the lesion reached the convexity of the frontal lobe, and the cortex on the orbital surface posterior to this point was free from injury. At this level the lesion extended through the white matter just above the caudate nucleus with only a millimeter of tissue intervening. On the convexity the lesion passed superiorly just anterior to and above the anterior subcentral sulcus. It passed along the anterior margin of the precentral convolution, superiorly along the anterior margin of the precentral sulcus. The cortex on the anterior margin of the lesion on the convexity of the brain was area 6 in all but a small zone in the upper third of the precentral convolution where gliosed area 4 was present. There was a small lesion of the postcentral convolution in the face area, part of which was apparently the result of terminal experimentation.

Thalamus—in the white matter around the head of the caudate nucleus there was ex-

tensive degeneration, indicated by a marked gliosis. This extended into the rostral portion of the corpus callosum. The degeneration of the deep white matter of the frontal pole could be traced posteriorly into the white matter of the temporal lobe and into the white matter lying just lateral to the angle of the body of the lateral ventricle. In these locations the degeneration became diffuse and could not be followed as a bundle. A massive degeneration descended in the anterior limb of the internal capsule and then divided into two groups of degeneration. The first swung medially at the oral extremity of the thalamus and entered the nucleus ventralis anterior, spreading out along the internal medullary lamina. Many normal cells were present in the gliosed nucleus ventralis anterior, but as this portion of the thalamus was followed posteriorly a definite decrease in cells was noted—evidence of retrograde cell degeneration of the dorsomedial part of the nucleus ventralis lateralis. The majority of the fibers passed through the internal medullary lamina into the nucleus medialis dorsalis of the thalamus, which except for scattered normal cells was severely degenerated throughout its entire extent (fig 58). The anterior thalamic nuclei on both sides showed a slight scattered degeneration in the nucleus anteroventralis in its middle and lower parts. The nucleus ventralis posterior was not degenerated. The second group of degenerated fibers, which passed through the anterior limb of the internal capsule, reached the basis pedunculi. Some seemed to enter into the region of the nucleus ruber, where considerable gliosis perhaps indicated their termination. The majority of the fibers passed along the medial part of the cerebral peduncle into the pons (Arnold's bundle).

It is apparent from this case that in the chimpanzee there is a relatively rich projection from the dorsal and medial portions of the ventrolateral nucleus of the thalamus to area 6. Presumably the remainder of the ventrolateral nucleus of the thalamus (which degenerates when the entire frontal cortex is removed—chimpanzee Mussai) projects to the precentral cortex that remained in this animal, namely area 4 and part of area 6. Thus area 4 receives its afferent fibers mainly from the posterior and lateral parts of the nucleus ventralis lateralis.

Area 4 may be divided into face, arm, and leg fields. The projection to each from the thalamus is fairly well established. Although Dejerine and

certain earlier investigators suggested that the somatotopic orientation
within the ventral nucleus of the thalamus is vertical, it has been shown
by several methods that the body segments are represented horizontally.
In 1934 this mediolateral arrangement was demonstrated for the macaque
monkey (Walker, 1934) by Nissl's method. Three years later Dusser de
Barenne and Sager (1937) confirmed this representation using the strych-
ninization method. Further verification has been made anatomically by
Le Gros Clark and Boggon (1935). The face field of area 4 receives the
fibers from the more medial portion of the ventrolateral nucleus, the arm
field from the central portion, and the leg area from the lateral or para-
lamellar portion of the ventrolateral nucleus of the thalamus Anatomi-
cally there appears to be a certain amount of cortical overlap between
these projections. This somatotopic arrangement is present in the chimpan-
zee (Walker, 1938b, Exp 3 and 7). That this probably holds for man also
may be deduced from the degenerations found in case 1 of this report.

Area 4s—The thalamic projection to area 4s cannot be defined at
this time. In the macaque monkey this area is so small that little retro-
grade cell degeneration would be expected from a lesion confined to it In
one chimpanzee ("Suzanne" case 3) an isolated lesion of this area failed
to produce degeneration in the thalamus. In fact, it seemed that the de-
myelinized fibers could be traced only to the cingular gyrus, and no
degenerated fibers could be followed to the thalamic region. Polyak (1932),
however, shows a projection to the anterior part of area 4. It is probable
that the "strip area" receives few, if any, fibers from the thalamus. The
afferent connections to this area have not been studied in man, so no state-
ment can be made regarding its thalamic projection.

Area 6—The thalamic projection to area 6 becomes progressively
larger as one ascends the phylogenetic scale. In the macaque monkey only
a few fibers from the thalamus enter the upper and lower parts of area 6
(Walker, 1938a, Exp 9 and 11) In the chimpanzee a much more extensive
thalamic projection to the premotor area is present (see chimpanzees
"Becky" and "Lucy," Walker, 1938b). The following case illustrates the
afferent connections to this area from the thalamus in the chimpanzee.

CASE 3

An immature female chimpanzee ("Su-
zanne") was subjected to the following
operative procedures
  March 13, 1936 Ablation of the right
cerebellar hemisphere
  April 22, 1936 Ablation of the left pre-
motor area.

January 22, 1937 Ablation of the strip
between areas 4 and 6 on the right side
  February 4, 1938 Ablation of right pa-
rietal lobe
  October 25, 1939 Ablation of left parie-
tal lobe
  Four days after the left parietal lobe was

removed the animal died As only the frontal lobe lesions are pertinent to this discussion the other ablations will not be described

Description of the Right Cerebral Hemisphere

The right cerebral hemisphere was about the same size as the left and contained two lesions both of which appeared to be of some age, for they were free of blood, and covered by thin, brownish arachnoid The first lesion lay in the frontal lobe and the second in the parietal lobe

Extending from the midline about one centimeter in front of the central sulcus was a narrow slit varying from 2 to 6 mm in width which passed almost vertically downward to join the central sulcus at its anterior curve, about 1.5 cm from its lower extremity The lesion extended downward on the medial surface of the hemisphere for 0 6 cm The precentral convolution was narrowed, but its surface was not injured The prefrontal area anterior to the lesion was normal

An examination of serial sections of the brain revealed a shallow lesion of the precentral convolution destroying all layers of cortex but not damaging the walls of the inferior precentral sulcus Farther posteriorly it reached the anterior lip of the central sulcus The lesion then passed dorsally to the superior precentral sulcus, the lip and walls of which were little damaged Farther superiorly, however, the narrow lesion extended to the white matter and reached the midline The lesion was bounded on the anterior margin largely by cortex of area 6, and on the posterior margin mainly by area 4 cortex It had therefore damaged the cortex adjoining these two areas, referred to by Hines (1937) as the "strip area" and by Dusser de Barenne and McCulloch (1938) as area 4s (fig 59)

From the lesion no degeneration could be traced through the internal capsule to the thalamus The major portion of the demyelinization passed medially, leaving a narrow band of "U" fibers intact, to reach the gyrus cingulum (fig 60)

Description of the Left Cerebral Hemisphere

The convexity of the left cerebral hemisphere was largely obscured by a thin layer of hemorrhage, making the accurate delimi-
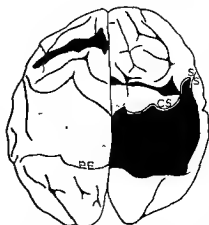
Fig 59 (Case 3)—Sketch of the cerebral hemispheres of chimpanzee "Susanne," to show the extent of the cortical lesions The stippled area on the right side represents a small zone of subpial softening, that on the left side, the ablation made just before the death of the animal

tation of the lesion difficult Two lesions were present —presumably quite fresh, for its bed was necrotic and hemorrhagic white matter—in the parietal lobe, and the other in the premotor region The extent of the latter lesion was difficult to map, owing to the subarachnoid hemorrhage It was a wedge-shaped lesion extending from the midline to the tip of the central sulcus Its posterior margin at the midline was 2.2 cm anterior to the central sulcus; inferiorly it was 1 2 cm anterior to the central sulcus The lesion was 2 0 cm in width at the midline, and 1 0 cm in width at its inferior extremity The crater was depressed 0.5 cm below the surface of the surrounding cortex From the midline the lesion extended 4.0 cm laterally and onto the medial surface for 1 0 cm The lesion lay just anterior to the sulcus precentralis superior and followed the posterior lip of the sulcus precentralis inferior Anteriorly it cut across the sulci frontalis superior and inferior

Examination of serial sections of the left hemisphere showed the lesion to be a relatively superficial one, extending from the midline across the middle frontal sulcus It was wider along the midline than laterally Medially it reached the dorsal lip of the calloso-marginal sulcus and had produced a small softening beneath the cingu-

Fig 60 (Case 3) —Photomicrograph of the paracentral region to show the degenerated fiber tract entering the cingular gyrus from the lesion of area 4 (Smith-Quigley stain for myelin)
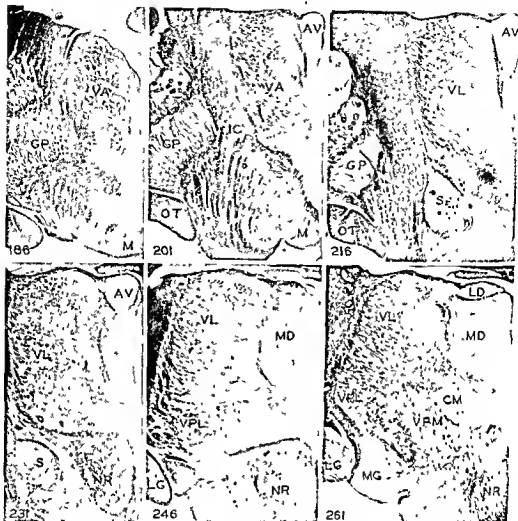
Fig 61—Photomicrographs of six representative serial sections of the left thalamus of chimpanzee 'Suzanne,' with the retrograde cell degeneration indicated by stippling (Smith Quigley stain for myelin)

In gyrus It extended into the white matter only one or two millimeters and did not damage the cortex or the walls of the superior or middle frontal sulci The anterior margin of the lesion was bounded in most sections by area 6 although it intruded upon area 8 in places The posterior margin of the lesion was bounded by area 6 The lesion therefore had damaged the anterior part of area 6 involving area 8 only slightly (fig 59)

Thalamus—The retrograde cell degeneration in the left thalamus was confined to the dorsal half of the nucleus ventralis lateralis Anteriorly it was somewhat scattered, but just caudal to the anteroventral nucleus it was both extensive and intense It did not involve the medial part of the nucleus and hence did not reach the internal medullary lamina It disappeared at the level of the rostral part of the nucleus centrum medianum (fig 61)

In the human being the thalamic projection to area 6 appears to be still more intensive Stern's study (1942) is the only example of an ex-

tirpation in man of area 6 in which the thalamic degeneration has been studied. In his case the extirpation for removal of a cerebral scar was placed quite far anteriorly, but there was extensive degeneration of the ventrolateral thalamic nucleus (fig. 62), probably due to involvement of area 6 by the pathological process. This increasing augmentation of the thalamic projection to area 6 correlates well with the development of this area in ascending phylogeny.

The topical arrangement of the projections from the thalamus to the cortex of area 6 probably parallels that to area 4. Thus lesions involving the medial portion of area 6 would give rise to degenerations in the more
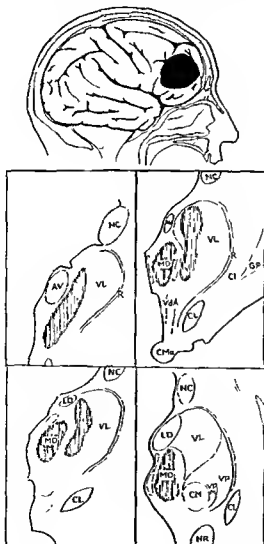
Fig. 62.—Sketches of the lesion and retrograde cell degeneration in the thalamus in Stern's case (1912). (*By permission of the Journal of Anatomy*)

lateral portion of the ventrolateral nucleus of the thalamus; whereas lesions involving the lateral portion of area 6 would cause degeneration in the medial portions of this nucleus.

Area 44—Relatively little is known of the thalamic projection to area 44 in the higher primates. In the macaque monkey it receives few fibers. In the chimpanzee data are lacking, and in man nothing is known of its thalamic connections.

Area 8—From the data available in the macaque monkey, area 8 appears to receive its thalamic projection from the nucleus medialis dorsalis rather than from the ventrolateral nucleus. In the chimpanzee and in man no data are available directly bearing on this subject. There appears to be a certain topical localization within the projection to area 8, the upper portion of area 8 receiving fibers from the upper and lateral portion of the dorsomedial nucleus, and the lower portion of area 8 receiving fibers from the medial and inferior parts of the dorsomedial nucleus.

Area 47 (area orbitalis dysgranularis; area 13 of Walker, 1940b)—The thalamic projection to this area is based mainly upon observations on the macaque monkey. Lesions of the orbital surface of the frontal lobe produce marked degeneration of the medial portion of the nucleus medialis dorsalis. In several chimpanzees, following extensive frontal lobectomies, similar degenerations have been found, presumably due to damage of this area, but more localized lesions are necessary to be certain of this point.

Area 24 (anterior limbic area)—Although Lashley (1941), Waller (1934), and Le Gros Clark (1932) found that the anteromedial nucleus sends fibers to area 24 in the rat, there is little evidence to suggest that this area receives a strong projection in primates. In the monkey only slight cellular changes were found in the nucleus anteromedialis after a frontal lobectomy (Walker, 1938a, Exp. 7). In one animal a large lesion of the medial surface of the hemisphere damaged a considerable part of area 24 without causing any detectable cellular change in the thalamus. In chimpanzee 'Becky' mild changes were present in the nucleus anteroventralis. Most of area 24 was removed in this case. In man there is no evidence bearing upon this point. Although cases are reported (Dejerine, 1895) in which the anterior nucleus was degenerated, lesions were not present in area 24. It therefore seems that area 24 receives few, if any, fibers from the thalamus.

Afferent Fibers from Other Subcortical Centers

It has been stated by a number of different investigators that various other subcortical structures project upon the cerebral motor cortex. The red nucleus (Monakow, 1905; Jelgersma, 1918), the striatum (Cajal, 1911), and other subcortical centers have been claimed to send fibers to the cer-

cbral cortex. However, the recent volume of work on the cerebral cortex has failed to confirm these findings. Until more evidence is presented, the existence of such fibers must be considered as questionable.

Significance of Afferent Connections

The richness of the afferent supply to the precentral convolutions indicates the importance of this area as a cortical effector center. Coming from many sources, the afferent fibers are obviously not all of the same functional order. Those originating from other cortical areas probably represent connections which serve to initiate or inhibit a motor response. Those coming from subcortical centers seem to be concerned with other functions.

The subcortical projection is largely derived from the nucleus ventralis lateralis of the thalamus, which in turn is the main receptor of the fibers of the brachium conjunctivum (Walker, 1938a). This cerebello-rubro-thalamo-cortical hookup has been suggested by many investigators, but only recently has it been conclusively demonstrated. What type of impulses it carries, precisely the effect of these impulses on the cerebral cortex, and how they influence the motor mechanism is not known. There is no evidence that this pathway carries any modality of conscious sensation. Frequently it has been stated that it subserves "unconscious proprioception," but this philosophical phraseology merely obscures the issue. The main influence of the cerebellum on the cerebral cortex has been related to the maintenance of proper tone within the individual units of the motor system. The removal of this influence leaves the cerebral cortex in an abnormal state (Dusser de Barenne and McCulloch, 1941a), and this in turn produces an abnormal tone, including tremor, in the peripheral musculature. This mechanism does not enter consciousness. If the maintenance of tone were the only function of the thalamic projection, conscious sensations would not be produced by stimulation, nor sensory loss by extirpation of the precentral motor cortex. Yet both of these phenomena do occur.

Penfield and Boldrey (1937) have reported an extensive series of cases in which the cerebral cortex was stimulated electrically. Sensation, mainly of tingling, numbness, or a sense of movement, was produced by excitation of the precentral and postcentral convolutions, and approximately 25% of the responses were obtained from the precentral convolution. It is true that in these cases the postcentral convolution was intact and that it could conceivably have been responsible for the result, either due to direct or indirect stimulation. Yet this seems unlikely. One type of response, a "desire-to-move," was obtained almost exclusively from the precentral cortex. Extirpation of the precentral cortex, as has been stated many times, pro-

duces initially sensory disturbances which usually clear up within a few weeks (Evans, 1935). The modalities most frequently involved are pallesthesia, proprioception, and stereognosis. Usually the appreciation of pin prick and cotton wool is good, although the latter may be poorly localized. Is this absence of impairment of tactile sensation to be correlated with Marshall, Woolsey, and Bard's (1938) finding that tactile representation in the monkey is exclusively in the parietal lobe? That these sensory disturbances are the result of edema of the postcentral convolution does not seem likely, for frequently when only an arm or face field is removed the uninvolved limb retains normal sensibility, although both its motor and sensory cortical field adjoin the ablation. It seems evident, therefore, that there is a conscious sensory representation in the precentral motor cortex. (See also Chapter XIV.)

Is this representation subserved by the fibers from the ventrolateral nucleus, or is it a clinical manifestation of the dual thalamic projection from the nucleus ventralis posterior, which has been discussed previously (p. 121)? Although the first hypothesis is possible, the fact that the sensation obtained from stimulation of the pre- and postcentral convolutions is identical, except for the phenomenon of "desire-to-move," favors the second suggestion. The second alternative allows a rational explanation for the rapid disappearance of the sensory disturbances.

The significance of the afferent connections of the precentral motor cortex is then threefold. In the first place, through the fibers originating from other cortical areas it receives excitatory or inhibitory impulses. May the "desire-to-move" phenomenon excited by cortical stimulation be the artificially induced counterpart of this first type of impulse? Secondly, through the cerebello-rubro-thalamo-cortical system the precentral motor cortex is kept in a constant excitatory state, the peripheral manifestation of which is "tone." And finally by fibers which probably originate in the nucleus ventralis posterior of the thalamus the precentral regions acquire a sensory representation qualitatively of the same order as that attained in the postcentral convolution.

Chapter V

EFFERENT FIBERS

Paul M. Levin, M.D.

Assistant Professor of Neuropsychiatry
Southwestern Medical College
and
Attending Neurologist
Texas Children's Hospital
Dallas

OUTLINE OF CHAPTER V

Efferent Fibers

EFFERENT FIBERS

T HE PRECENTRAL REGION of the cerebral cortex was recognized early as the source of a great cerebral efferent tract, the cortico-spinal or so-called "pyramidal tract" of Türck and Flechsig. Although it has been known for many years that other corticifugal fiber systems originate in the cerebral cortex, indeed in this "motor" region, the importance of these extrapyramidal tracts has not been generally recognized until the past decade. It is readily apparent from the pronounced decrease in size of the corticifugal bundle as it passes through the brain stem that the extrapyramidal projection of the cerebral cortex is much more extensive than the pyramidal system.

The following description of the efferent fibers of the precentral cortex is based mainly upon human pathologic data and experimental studies of primates, with mention of certain findings in lower animals. As a preface to this review, a brief discussion of the chief technics employed is presented.

Methods of Tracing Nerve Tracts

Marchi Method—This is the most important method by which degenerating myelinated nerve fibers may be traced. It is a highly sensitive method, requiring the utmost precautions in limiting the experimental lesion to the area studied, in the performance of the histologic technic, and in the discretional study of the preparations. It is not always satisfactory for fine myelinated fibers and, of course, does not reveal changes in unmyelinated fibers.

Fiber Degeneration by Weigert's Method (or any other method for staining intact myelin sheaths)—This method, demonstrating an absence of myelin after degeneration of a fiber tract, is of value particularly when the tracts are compact and heavily myelinated. In the study of small bundles of fibers, or when the fibers of a tract intermingle with those of other tracts, the method loses much of its value. A complement of this technique is the demonstration of gliosis in the bed of a degenerated tract. With the use of silver impregnation for axis cylinders instead of the myelin stain, the total fiber content, including the unmyelinated, may be studied.

Retrograde Cell Degeneration of Nissl—Chromatolysis of the Nissl substance in ganglion cells, following interruption of their axons, provides an accurate method of tracing the origin of a fiber tract. It has several important limitations. There is an optimum period for the chromatolysis, which appears to differ in the various tracts of the brain; therefore, the

time factor must be determined separately for each system studied. If the central axonal segment provides collateral branches, the retrograde alteration may be significantly modified. Further, the reaction is difficult to detect in ganglion cells that are not highly chromatophilic, and in certain nuclei related to the vegetative nervous system the normal cell appearance approaches that of the axonal reaction. Chromatolysis from other causes, such as diffuse circulatory disorders (shock is an example), has to be differentiated by histologic detail and a widespread distribution. With these qualifications, the method has much value, but only when it yields positive results.

Projection Fibers

The efferent projection fibers of the precentral region of the cerebral cortex form a dense mass which descends into the underlying segment of the corona radiata. The course of these fibers has been studied by numerous investigators during the past half-century. Mellus (1899) and Simpson (1902) studied Marchi preparations with lesions of the precentral region, with consistent results which since have been amply confirmed. In recent years the projection systems of the cytoarchitectural areas 4, 6, and 8 were examined by Levin (1936); area 4, by Hirasawa and Kariya (1936); areas 4, 4s, and 6, by Verhaart and Kennard (1940). These investigators found by the Marchi method that the efferent fiber tracts of these areas are intimately related—not only do they intermingle, but also they pass to the same subcortical nuclei, except for the spinal projection which is essentially derived from area 4. The descending projection fibers pass exclusively into the ipsilateral internal capsule and do not decussate through the corpus callosum (Polyak, 1932).

The mass of precentral corticofugal fibers passes medially, downward, and slightly posteriorly and enters the internal capsule, where it occupies the anterior two-thirds of the posterior limb (fig. 63). A spatial distinction of the fibers from areas 8, 6, 4s, and 4 is already evident, although there is considerable overlap (fig. 64). The fibers from area 8 are situated close to the knee of the internal capsule, those from area 6 immediately posteriorly, and those from area 4 in the middle part of the posterior limb. It has been stated also that the leg fibers are situated posterior to the arm and face fibers in the internal capsule, and lateral to them in the cerebral peduncle. The plan of this chapter is to follow these fibers as they leave the main avenue of the descending tracts toward their destination in various subcortical nuclei.

Cortico-Striatal Fibers—Lesions in the precentral areas give rise to degeneration in minute fibers of the stratum subcallosum in the region of
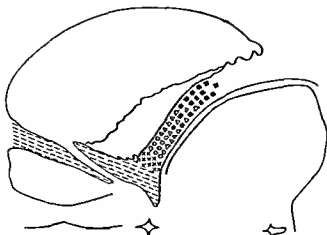
Fig 63 —Diagram of the distribution of the frontal efferent fibers in the internal capsule of the monkey Horizontal section Area 4 fibers are represented by squares, area 4s, by triangles, area 6, by circles, area 8, by 'x , and prefrontal region, by broken lines The fibers from the precentral region occupy the anterior two-thirds of the posterior limb with those from area 8 situated immediately posterior to the genu, and those from areas 6, 4s, and 4 farther posterior The partial intermingling of the fibers from these areas is indicated

passage of the precentral efferent systems. Sachs (1897), Dejerine (1901), Minkowski (1923-1924), and Polyak (1932) considered the stratum subcallosum to be the pathway of descending fibers from the cortex to the caudate nucleus. However, most observers have found no degenerated fibers within the caudate nucleus, even when the subcallosal degeneration was heavy. Glees,[1] on the other hand, noted in the cat that destruction of an area comparable to area 4s in primates resulted in degeneration of the fine unmyelinated nerve network in the caudate nucleus. This observation lent anatomical confirmation to the demonstration by Dusser de Barenne, Garol, and McCulloch (1940), in their electro-physiological studies, that the suppressor areas 4s and 8 send fibers to the caudate nucleus.

Dusser de Barenne, Garol, and McCulloch also demonstrated a projection from areas 4 and 6 upon the putamen (which in turn activates the outer segment of the pallidum). This physiological observation has likewise been confirmed by Glees (1944, 1945) who presented anatomical evidence of projection fibers from area 4 to the putamen and from area 6 to the external segment of the globus pallidus. Unquestionably, further research is needed to clarify, amend, and amplify our knowledge of the cortico-striatal fibers.

Cortico-Pallidal Fibers—As the projection from the precentral cortex passes farther along in the internal capsule it comes to lie along the medial border of the globus pallidus The gray matter of this nucleus, particularly

[1] Glees, P Personal communication to Dr W S McCulloch

of its inner segment, encroaches upon the fibers of the internal capsule and divides the marginal fibers into small bundles. Although the degeneration in these bundles has led some to infer that they represent cortico-pallidal fibers, recent studies show that the fibers for the most part do not terminate here but rejoin the internal capsule, even after a considerable deflection (Levin, 1936; Verhaart and Kennard, 1940). However, a fine stippling may be noted around the bundles, suggesting that fibers are here given off, possibly as the fine collaterals of the descending fibers described by Cajal (1911). The myelogenetic findings of Flechsig (1921) suggested abundant connections between the central cortex and the globus pallidus, but other investigators (as Wilson, 1914) have been unable to demonstrate these fibers. However, McCulloch and his collaborators have found definite electro-physiological evidence that area 6 projects directly onto the globus pallidus (see Chapter VIII), and Glees (1945) reports finding anatomical evidence of fibers from area 6 to the external segment of the globus pallidus.

Cortico-Thalamic System—There is an extensive projection of the cerebral cortex upon the nuclei of the thalamus. This projection is well organized (Monakow, 1905) and closely parallels the thalamo-cortical

| Area 4 | Area 4s | Area 6 | Area 8 | Prefrontal |
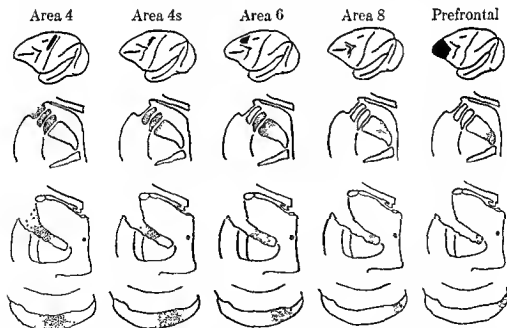
Fig. 64—Diagrammatic presentation of the projection systems of the precentral area showing cortical lesions placed within each of these areas and the location of the degenerated fibers in the internal capsule and cerebral peduncles. In the column on the right a lesion and the fibers of the prefrontal region are added for the sake of completeness. In the diagrams of the internal capsule and the peduncle the medial part lies to the right, the lateral to the left, in each instance.

system. From all the precentral cortical areas, a moderate number of medium and fine fibers enter the thalamus beginning at about the transverse level of the anterior commissure. They form part of the radiating fibers of the lateral nuclear mass (Simpson and Jolly, 1907; Sachs, 1909; Polyak, 1932) and extend throughout the ventral lateral nucleus. This is the portion of the thalamus which, according to Walker (1938a), receives the fibers of the brachium conjunctivum and projects upon the motor cortex, thereby completing the chain of the cerebello-thalamo-cortical pathway. The interrelation of the short cortico-thalamo-cortical circuit with the longer cortico-ponto-cerebello-dentato-thalamo-cortical circuit is not understood. Another function of the cortico-thalamic fibers, according to Riese (1925), may be in relaying impulses to the striatum; a thalamic link in the cortico-hypothalamic pathway is likewise to be considered.

Cortico-Hypothalamic Connections—Anatomic evidence of a direct pathway from the precentral cortex to the hypothalamus is very scant, in spite of the physiologic observation of autonomic activity of this cortical region (see Chapter XI). Mettler (1935b) saw degeneration of fine myelinated fibers in the septum pellucidum after a lesion of the precentral gyrus, and Hines (1943) noted fibers passing to this region after injury of area 4s. Levin (1936) did not observe clear Marchi degeneration into the septum with lesions of the precentral or prefrontal areas except when the olfactory tract was damaged. According to Ariens Kappers, Huber, and Crosby (1936), direct cortico-hypothalamic tracts arise only in the olfactory cortex, i.e., the hippocampus. The observation by Kimmel (1943) of a projection of the substantia nigra upon the mammillary body, infundibulum, and lateral hypothalamic area suggests nigral relay in a precentro-hypothalamic system.

Cortico-Zonal and Cortico-Rubral Fibers—A small number of fibers from the precentral cortex leave the internal capsule and sweep into the ventral tegmental field of Forel (H_1) and zona incerta. These fibers are derived from areas 4, 4s, and 6. The degeneration in the zona incerta consists of a fine stippling, suggesting changes in terminal arborizations; that which passes in H_2 with the lenticular fasciculus is coarser, and the Marchi granules are arranged in long rows characteristic of true secondary degeneration. The degeneration continues caudally into the superior radiation of the red nucleus, and it is probable that the fibers represent percentrorubral as well as precentro-zonal fibers. The changes in the red nucleus are limited to the anterior (microcellular) portion. Fibers cannot be traced into the subthalamic body of Luys. Cortico-subthalamico-rubral fiber degeneration has been observed by numerous investigators, including Monakow (1910), Archambault (1914-1915), Minkowski (1923-1924), Levin

(1936), and Hirasawa and Kariya (1936) However, it is only mild, and corticifugal fibers form only a small part of the fiber systems of this region This confirms the work of Edinger and Fischer (1913), who found the subthalamic fibers little changed in an essentially decorticate specimen with intact globus pallidus.

Arrangement in the Cerebral Peduncle—In passing through the internal capsule the mass of fibers from the precentral cortex has given off a moderately large number of fibers. The fibers to the diencephalon are mostly fine and medium in thickness. The remaining fibers, consisting of large numbers of thick fibers in addition to many smaller ones pass into the cerebral peduncle, where they occupy the larger part of the pes peduncli. The precentral corticifugal mass lies between Arnold's bundle (from the prefrontal cortex), in the medial one-tenth of the pes, and Türck's bundle (the origin of which is still doubtful, although it probably arises from the parietal cortex—see Mettler, 1935c; Rundles and Papez, 1938; and Peele, 1942c), in the lateral one-fourth. The projections of the constituent areas are still arranged in an orderly fashion, the medial fibers being a small bundle from area 8, with larger bundles from areas 6, 4s, and 4 respectively, distributed more laterally (fig. 64) The relative magnitudes of the projections from areas 4, 4s, and 6 have not been accurately determined, but the impression is gained from the various reported studies that area 4 has the greatest total projection area 4s is probably next, and area 6 has the least In one of Levin's experiments (1936; Exp 9), in which the lesion involved the anterior portion of area 6 (6aβ of the Vogts), the degeneration was much less than in others in which the lesions were located in the posterior portion of area 6, probably including also part of area 4s.

Cortico-Nigral Tract—In the midbrain, numerous fibers of medium and fine caliber stream dorsally from the pes peduncli, forming the stratum intermedium peduncli A short distance after leaving the main corticifugal band they disappear into the substantia nigra Isolated fibers pass through the substantia nigra, disappearing at the border of the reticular formation. These changes occur at all levels of the midbrain but are usually more pronounced in the caudal portion They are not apparent in the rostral (diencephalic) portion of the substantia nigra

The cortico-nigral tract is one of the major efferent pathways from the precentral region. Approximately one-third of the precentral corticifugal fibers descending to the midbrain pass into the stratum intermedium directly dorsal to the degenerated segment of the pes peduncli. The degeneration in the stratum intermedium varies with the size and location of the cortical lesion.

This direct cortico-nigral system of fibers may be considered as definitely established by numerous studies on a variety of animals and man. Dejerine (1901) described it well and specified the precentral gyrus as the main origin of this tract in man. Mellus (1899) and Jolly and Simpson (1907) indicated degeneration of cortico-nigral fibers after precentral lesions in monkeys, and Monakow (1914) described such degeneration in human cases with extensive cortical defects, especially of the operculum Economo (1902), in the rabbit, traced fibers to the nigra from the cortical area for chewing Minkowski (1923-1924), Polyak (1932), Levin (1936), Hirasawa and Kariya (1936), and Verhaart and Kennard (1940) are in complete accord in presenting the cortico-nigral tract as described. They receive interesting confirmation in the embryologic observations by Cooper (1946) that the nigra (and pontine nuclei) develop from the midventral proliferation in intimate relation with the descending cerebral fibers of the peduncle, according to the principle of neurobiotaxis. However, Mettler (1935b) found no precentro-nigral projection and Riese (1925) held that such a connection is very questionable.

Do the cortico-nigral fibers constitute a separate tract or are they collaterals of other major pathways, such as the cortico-spinal and cortico-pontine systems? Cajal (1911) favored the latter view as a result of his work on normal specimens. Studies of experimental material, however, indicate that the portions of the cerebral cortex giving rise to the cortico-nigral and the cortico-spinal tracts, respectively, are dissimilar; the latter tract is largely derived from area 4, while the former takes its origin from areas 4s, 6, and 8 as well. In the precentral projection the cortico-nigral fibers show a closer correlation with the cortico-pontine tract, both as to their areas of origin and as to the relative amounts of degeneration in each resulting from small cortical lesions. Whether this similarity holds for other areas of the cortex is not clear; that it may not is suggested by Dejerine's observation (1901) that cases with degeneration of Türck's bundle show only doubtful nigral degeneration

It may not be out of place to discuss here the course of fibers arising from the substantia nigra. That the major projection of the nigra is upon the corpus striatum is indicated by the studies of Riese (1925) and Ferraro (1925 and 1928). Both of these investigators found extensive retrograde degeneration in the cells of the substantia nigra following subtotal destruction of the striatum. With the Weigert method, Rundles and Papez (1937) traced fibers from the neostriatum to the substantia nigra. The experiments of Ranson and Ranson (1941) with peduncular lesions in the monkey, studied by the Marchi method, are very clear. These workers demonstrated secondary degeneration of fibers passing from the substantia

nigra rostrally through the pes pedunculi and internal capsule to the globus pallidus. Hemisection of the rostral end of the pons did not result in any such degeneration, nor did lesions of the striopallidum. The nigro-striatal nature of these fibers may thus be accepted (cf. Glees and Wall, 1946). Bucy (1942) has suggested that by continuing to the thalamus, and thence back to the precentral cortex, these impulses complete a neuronal circuit, cortico-nigro-pallido-thalamo-cortical (see Chapter XV).

Cortico-Pontine Tracts—As the fibers of the cerebral peduncle descend into the anterior hind-brain segment, they divide into several large bundles which interdigitate with the nuclei and fibers of the pons. An extensive projection of the cerebral cortex upon these nuclei is evident from the abundant fine degeneration of fibers in the ipsilateral gray matter of the pons after lesions of the cerebral cortex (Simpson, 1902), and from the pronounced decrease in size of the fiber bundles as they pass into the bulb (Mellus, 1899).

Much work has been done concerning the origin and distribution of the cortico-pontine tracts. The fronto-pontine tract (Arnold's bundle) and parieto-pontine tract (Türck's bundle) have received most of the attention. Dejerine demonstrated that many of the cortico-pontine fibers arise in the precentral region, but these have been usually considered to follow the course of Arnold's bundle (Winkelman and Eckel, 1926). As recently as 1936, Ariëns Kappers, Huber, and Crosby (p. 811) stated that the cortico-pontine tracts "come from association areas rather than from projection areas."

This neglect of the rolandic zone in the cerebro-cerebellar system is not warranted, as the precentral cortico-pontine tract is extensive. Experiments with the Marchi method indicate that it arises from areas 4, 4s, and 6 and passes through the posterior limb of the internal capsule and middle segment of the cerebral peduncle (Levin, 1936; Verhaart and Kennard, 1940). The chief difference between the portions of the tract arising in these areas is topical. The area 4 fibers pass into the middle of the descending bundles in the pons and terminate about the central pontine cells. The fibers from area 4s and from area 6 are more dorsomedial and terminate more rostrally and medially in the pons. The fibers from the anterior portion of area 6 and area 8 are fewer and finer than those from the rest of the precentral region.

The prefrontal origin of Arnold's bundle would seem to have been conclusively settled for the monkey by the observation of Rütishäuser (1899) on the degeneration following ablation of the anterior prefrontal region, well ahead of area 8. He found demyelinization of the medial segment of the cerebral peduncle (Arnold's bundle). The degeneration passed through

the anterior limb of the internal capsule and disappeared at rostral levels of the pons. (This study was made with Weigert's method, which does not produce the artifacts frequently seen with the capricious Marchi technic.) From human pathologic material, Monakow (1905) also considered an anterior prefrontal origin of Arnold's bundle, and Levin (1936) concurred on the basis of Marchi studies of the monkey. Verhaart and Kennard (1940) and Sunderland (1940), however, noted Marchi degeneration of the medial one-fourth, including the tip, of the basis pedunculi after lesions of area 6.

Mention should be made of a fiber bundle which in occasional specimens passes from the bulbar pyramid around the inferior olivary nucleus to the pontobulbar body. Since the pontobulbar body, which is situated near the restiform body, is considered to represent displaced pontine nuclear tissue, these circumolivary fibers of the pyramid constitute an aberrant cortico-pontine bundle (Swank, 1934). The precise origin of this bundle is unknown; the passage via the bulbar pyramid cannot be taken as necessarily indicating an origin in area 4.

Cortico-Tegmental and Cortico-Nuclear Fibers—Two routes have been suggested as the pathway of corticifugal fibers to the cranial nerve nuclei: a bundle of fibers passing near the medial lemniscus, and isolated fibers passing directly from the basal fiber-mass of the brain stem into the tegmentum.

The dorsal fibers of the peduncle, forming the caudal fibers of the stratum intermedium, continue into the pontine region at the ventral border of the tegmentum, medial to the medial lemniscus. Schlesinger (cited by Bechterew, 1899a) described this bundle as being preserved in a case of syringobulbia with lemniscal degeneration, and noted its connection with the cerebral peduncle; he assumed it to be the central afferent pathway of the cranial nerves. However, most later workers have held it to be corticifugal in nature. It was named descriptively the Fussschleife by Flechsig (1876), with various translations of this name given by others. In man it is separated into a medial (or superficial) and a lateral (or deep) component. In the monkey this division is not so distinct, the fibers forming a continuous band across the width of the peduncle. Degeneration of this bundle in the monkey occurs with lesions of all precentral areas and is localized to the segment continuous with the affected portion of the stratum intermedium. Thus, the lateral segment, overlying Türck's bundle, escapes degeneration when the lesion is in the precentral region. The lateral of the degenerated fibers, i.e., those derived from the middle of the peduncle (zone of area 4 fibers), pass laterally into the dorsolateral pontine

gray; the remainder continue at the tegmental border and are divided among both the dorsal pontine cells and the ventral tegmentum. Some of the fibers cross the tegmental raphe into the opposite side. The tegmental fibers usually disappear in Marchi preparations at the level of the trapezoid body, although a slight degeneration continues in some cases into the bulbar lemniscus. In man the bundles have been found degenerated in cases of cerebral lesions (Bechterew, 1899a; Dejerine, 1901). Dejerine (1914) included them as the aberrant pyramidal tract which provides the pathway of cortico-nuclear fibers, and Papez (1940b) likewise described the lateral bundle as the cortico-bulbar tract. Riese (1925) felt that the medial fibers are derived from the cerebral cortex, but that the lateral bundle arises in the pallidum and passes into the tegmentum at a pontine level However, the relation of the lateral fibers to Turck's bundle suggests that these may have a common origin; more work needs to be done on this point

Cortico-tegmental fibers also pass directly from the basal corticofugal tract into the tegmentum. In the midbrain, a number of fibers penetrate the substantia nigra up to the border of the tegmentum, although they are not observed to extend deeply into this region. Area 8 seems to provide a greater proportion of its fibers for the tegmentum than area 6 or 4. In the medulla oblongata. after lesions of area 4 only, scattered degenerated fibers fan out from the pyramid into the tegmentum of both sides.

The importance of these two routes in the transmission of cortico-nuclear impulses has been widely discussed, especially in the older literature (Sand 1903) Hoche (1898), in a study of human material with the Marchi method, considered that fibers to the tegmentum pass both directly and through the lemniscal region. Dejerine (1901 and 1914) expressed a similar opinion Monakow (1910) and Winkler (1929) gave the pedunculus lemnisci, especially the medial tract, as the pathway of cortico-nuclear fibers to the eyes, face, etc In the monkey, Minkowski (1923-1924) and Verhaart and Kennard (1940) felt that the tegmental bundle is essentially an aberrant cortico-pontine tract. Kosaka (1901) and Hirasawa and Kariya (1936) described cortico-nuclear fibers leaving the basal pathway at the levels of the cranial nerve nuclei; they were not certain whether the lemniscal fibers are central cranial nerve fibers or a cortical extrapyramidal tract In the studies of Levin (1936) it seemed fairly clear that fibers pass into the tegmentum from the pes lemniscus, although others also pass ventrally into the pontine nucleus; in addition direct corticotegmental fibers leave at mesencephalic and bulbar levels Most workers have agreed with the observation of Simpson and Jolly (1907) that the fibers to the tegmentum seem to terminate ventral to the cranial nerve

nuclei. Contact with the final common pathway is probably effected by means of intercalated neurons.

McCulloch, Graf, and Magoun (1946) demonstrated a direct projection of area 4s upon the medial bulbar reticular substance by detecting triphasic potentials here following cortical strychninization. In this way the precentral cortex may control the motor inhibitory region of the bulbar tegmentum revealed by Magoun and Rhines (1945).

Cortico-Spinal Tract—When it reaches the medulla oblongata, the corticifugal mass has been markedly reduced in size, forming the pyramid at this level. It is quite evident from this reduction that what now may be called the "pyramidal tract" forms only a relatively small part of the total cortical projection, approximately equal in extent to the cortico-pontine and cortico-nigral tracts from the precentral region. It has been intimately mixed with these and the other corticifugal tracts from the motor area in the posterior limb of the internal capsule and in the middle segment of the cerebral peduncle and longitudinal bundles of the pons.

The cortico-spinal tract continues almost unchanged in size through the medulla oblongata, as the number of cortico-bulbar fibers that leave at this level is small. At the pyramidal decussation the bulk of this tract crosses into the opposite lateral funiculus and forms the crossed lateral pyramidal tract. Of the ipsilateral fibers, some descend in the anteromedial white column as the ventral uncrossed tract while the others mingle with the crossed fibers from the opposite cerebral hemisphere as the uncrossed contingent of the lateral cortico-spinal tract (Fulton and Sheehan, 1935). In the monkey, the proportions of these three divisions are: lateral crossed fibers, 85%; lateral uncrossed, 12%; anterior uncrossed, 3%. In man the number of pyramidal fibers which decussate is said to vary between 75 and 90 per cent; the anterior uncrossed tract seems usually more extensive than in the monkey.

In the spinal cord of higher mammals, the cortico-spinal fibers can be followed into the lowest sacral levels. Marchi preparations show a fine stippling of the intermediate lateral zone of the spinal gray adjacent to both the crossed and the uncrossed lateral pyramidal tracts. Degenerated axonal endings are also seen in this region (Hoff and Hoff, 1934). In the monkey, with few ventral pyramidal fibers, the anterior horns show no degenerative change. This is comparable to the lack of degeneration of cortico-nuclear fibers in the region of cranial nerve nuclei, and one may here also suppose that the pyramidal fibers terminate upon intercalated cells.

The classical studies of Holmes and May (1909), on the retrograde cell degeneration in the cerebral cortex following hemisection of the spinal

cord, demonstrate the origin of the cortico-spinal tract in area 4γ, in the giant and large pyramidal-shaped cells of Betz. Neuropathologic study of certain diseases of the motor system, such as amyotrophic lateral sclerosis, has suggested the possibility of a more extensive origin of this tract (Monakow, 1914; Schröder, 1914; etc.). Kennard (1935), with the Marchi method, and Hoff (1935), with the demonstration of altered axonal endings, suggested a spinal projection from area 6, but the later Marchi studies of Verhaart and Kennard (1940) disagreed. Minekler, Klemme, and Minckler (1944) showed a rather heavy degenerated bundle descending from a surgical lesion of area 6 in man, passing through the pyramid into the spinal cord, and Hines (1943) traced cortico-spinal fibers also from area 4s. Utilizing the method of retrograde cell degeneration after high cervical hemisection of the spinal cord, Levin and Bradford (1938) found in *Macaca radiata* changes characteristic of primary irritation in infra-granular cells, mostly in area 4, with a smaller number of specifically altered cells in areas 5, 3, and 2, and suggestively also in area 1. (These parietal changes were confirmed by Kennard, 1938a.) Counts of degenerated cells suggested that area 4 furnishes 80% of the cortico-spinal fibers. No retrograde degeneration was seen in the cells of areas 4s and 6. Study of the myelinated fiber content of the pyramid following frontal lobectomy in the monkey demonstrated persistence of heavy fibers in the lateral one-tenth and numerous fine fibers scattered throughout the tract. The heavy fibers, situated lateral to the degenerated precentral fibers, may be presumed to have their origin posterior to the central sulcus, in accordance with the topical arrangement of the corticifugal tracts; this was corroborated by Peele (1942c).

The persistence of numerous fine fibers throughout the pyramid after frontal decortication raises the question of a subcortical origin of a portion of the pyramidal tract. In 1914 Monakow stated that complete pyramidal degeneration does not occur with purely cortical lesions, but is present only when there is extensive destruction of the internal capsule and striatum. More recently Haggquist (1937) showed that only one-sixth of the fibers of the pyramid, especially the medium and thick ones, disappear after ablation of the precentral cortex. Lassek (1942c) studied also the effect of parietal lesions. Destruction of area 4 alone resulted in an average loss of 33% of the pyramidal fibers; when the lesion included also the postcentral region the fiber loss averaged 48%; and when only the parietal cortex was destroyed, there were 14% less fibers in the ipsilateral pyramid than in the contralateral. Lassek's findings thus indicate a greater contribution of the cortex to the pyramidal tract than does Haggquist's, and they also may be taken to confirm the origin of a part of the cortico-spinal tract in post-

rolandic areas, although the author was doubtful of this component. Although Swank (1936) found that decortication in the rabbit does not lead to total pyramidal degeneration unless the lenticular nucleus be damaged, recent studies on the monkey (Mettler, 1944) and man (Lassek and Evans, 1945) indicate a cortical origin for all pyramidal fibers, unmyelinated as well as myelinated. Lassek and Evans studied cases of hemispherectomy for tumor in which the basal ganglia were spared, but in their case with sufficient survival for complete degeneration, the tumor had invaded the basal ganglia and midbrain. Much work needs yet be done in an analysis of the origin of the fine fibers.[2]

As a result of the pathologic studies of Schröder (1914), Davison (1937, 1941), and others, and the experiments of Tower (1940) and Lassek (1942a), it has been inferred that the central portion of the cortico-spinal axon with its myelin sheath persists after transection at or below the level of the pyramid. It should be recalled that the pyramidal fibers intermingle with the numerous extrapyramidal fibers from area 4 and to a lesser extent with those from areas 4s and 6. They are, so to speak, diluted by the fibers terminating above the bulbar level; cortico-spinal fibers appear as a well-defined tract only after the other fiber systems have been "filtered" out at higher levels. Purely cortico-spinal fiber degeneration in the cerebral peduncle or internal capsule would thus result not in a focal loss of nerve fibers, but rather in a quantitative reduction in the number of fibers, if this could accurately be estimated. A slight and diffuse astrocytosis might be the only demonstrable clue to a healed retrograde degeneration.

Prepyramidal collaterals of the cortico-spinal fibers have been implicated as the basis of preservation of the central segment of these fibers after pyramidal section (Tower, 1940). However, studies with the method of retrograde cell degeneration are not in accord with this view. Hemisection at a rostral level of the pons, interrupting the fibers both to the pons and spinal cord, caused an axonal reaction in the medium and small pyramidal cells of areas 4 and 4s, leaving the giant and large pyramidal cells in several cases (with appropriate survival periods) appearing quite normal (Levin and Hayashi, to be published). These results are to be contrasted with the effects of lesions of the cortico-spinal tract alone, by hemisection of the spinal cord. Here the reaction is limited to the giant and large pyramidal cells, and does not extend into area 4s (Levin and Bradford, 1938). It may be concluded that the precentral projections to the pontine nuclei and to the spinal cord comprise distinct neuronal systems, differing in both the size and the distribution of the cells of origin.

[2] See also Chapter VI for a discussion of the composition of the pyramids.

Association and Commissural Fibers

The areas of the precentral region send numerous fibers to cortical areas in both cerebral hemispheres. Minkowski (1923-1924) divided the precentral association pathways into several groups: proper fibers connecting different areas of the precentral gyrus; intralobar fibers to the prefrontal region; and long association fibers to the parietal region and the first limbic convolution. In addition to these he noted commissural fibers passing through the corpus callosum to the opposite precentral and postcentral gyri (homogyric and heterogyric callosal fibers, respectively), in agreement with van Valkenburg (1913). Ariëns Kappers, Huber, and Crosby (1936) and Mettler (1935b) mention also long association fibers to temporal and occipital regions. However, Bailey, Garol, and McCulloch (1941b) and McCulloch and Garol (1941b) were unable physiologically to demonstrate commissural fibers from area 4, except from the "trunk," "neck," and "face" areas in the chimpanzee and in the monkey.

Summary

The efferent fibers from all areas of the precentral cortex follow a similar pathway through the posterior limb of the internal capsule and cerebral peduncle. They pass in small numbers to the striatum, thalamus, zona incerta, and red nucleus. The projection over the substantia nigra and pons is more extensive. The cortico-spinal tract from the precentral region arises exclusively in the motor area proper, area 4. Apart from this fiber tract, the differences between the projection systems of the precentral areas are mainly corticotopic, the fibers from the anterior areas being arranged more medially in the corticifugal pathway; in addition, the fibers from area 8 and the anterior part of area 6 are fewer and finer than those from the posterior areas of this region.

Chapter VI

THE PYRAMIDAL TRACT

Sarah S. Tower, Ph.D., M.D.

Instructor in Psychiatry
The Johns Hopkins University
Baltimore

OUTLINE OF CHAPTER VI

The Pyramidal Tract

THE PYRAMIDAL TRACT

DEFINITION AND STRUCTURE

ORIGINAL USAGE designated as "pyramidal" the fibers which make up the bulk of the medullary pyramids. When, in 1851, Türck first employed the term "Pyramidenstrang" he recognized the cortical origin of some of the fibers, but as late as 1876 Flechsig justified its use as not implying origin. In succeeding decades the application of Marchi and Weigert techniques to anatomical analysis confirmed the impression that the group of fibers thus designated pyramidal is a structural entity. Considering myelinated fibers only, it seemed to include all the fibers descending from the cerebral cortex to the spinal cord but no other fibers to the cord. Thus "pyramidal" became synonymous with "corticospinal." In the same period, however, the term pyramidal was also often extended to include those fibers from the cerebral cortex which bear a relationship to the cranial motor nuclei similar to that of the corticospinal fibers to the cord. And this seems reasonable. Currently, therefore, the term "pyramidal" may be employed in the restricted sense of corticospinal, or in the larger sense described, usually without leading to confusion.

Recently this simple concept of the composition of the pyramidal tract has become questionable, largely through the application of silver technique to the study of its fiber composition. From time to time it has been suggested that the medullary pyramids may contain fibers of other than cortical origin (von Monakow, 1915; Swank, 1936). These were studies with myelin stains. In another direction, McKibben and Wheelis reported in 1932 that unmyelinated fibers make up a large proportion of the medullary pyramids in the cat, a statement which should have received more consideration than it did. It remained for Lassek (1940, 1941, 1942) and Lassek and Rasmussen (1939) to open the new inquiry effectively.

Applying, for the critical part, silver technique and painstaking numerical assay, Lassek and Rasmussen (1939) first showed that the human medullary pyramid, like that of the cat, is made up in large part of unmyelinated fibers. The human pyramid contains roughly about a million nerve fibers just rostral to the decussation (half a million in the rhesus monkey), of which roughly 61 per cent are myelinated and the remainder unmyelinated. Moreover, of the myelinated fibers the great majority, 89.57 per cent, are small, 1 to 4 μ in diameter, and only 1.75 per cent are of large calibre, 11 to 22 μ. Lassek (1942b) calculated that there are in the human pyramidal tract about 30,000 fibers with a diameter of from 9 to 22 μ. Since it is the 10 per cent of fibers with a diameter of 5 μ and over which make

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up the pyramidal tract as it has ordinarily been considered, and which show up in routine Weigert and Marchi preparations, this work of Lassek and of Lassek and Rasmussen clearly poses the question, whether we can continue to consider as one tract the bulk of fibers which makes up the medullary pyramids. What is the origin, course, termination, and function of the horde of small fibers, and especially of the unmyelinated component? Have they sufficient in common with the large fibers, for which these facts are more or less known, to be grouped together as the pyramidal tract?

Origin

The question of origin is most crucial. The cortical origin of the pyramidal tract has been a subject of much investigation, using both retrograde cell changes in the cortex after lesion to the tract below, and Marchi or Weigert studies after lesions in parts of the cerebral cortex. The first type of study (Holmes and May, 1909) showed unquestionably that the giant cells of Betz, which chiefly characterize Brodmann's area 4 of the cerebral cortex, contribute their fibers to the pyramidal tract. Lassek (1940, 1942a) has, perhaps, said the last word on this subject. He showed that in man there are about 34,000 cells in area 4 of one side, of 900 to 4,100 square microns diameter, which correlates significantly with the 30,000 fibers of 9 to 22 μ diameter in one pyramid. Assuming that one cell contributes only one fiber to the tract, the Betz cells may be considered to give rise to 2 to 3 per cent of the fibers of one pyramid; probably to all the fibers of 9 μ diameter and over. Lassek further showed (1942c) that ablation of area 4 in the monkey, besides virtually eliminating the 2 to 3 per cent of large fibers in the pyramid, also reduced the total fiber count by 27 to 40 per cent. Therefore, area 4 must also contribute a much larger number of smaller fibers, presumably from smaller cells. Unfortunately these area 4 ablations were not adequately checked histologically to ensure their completeness, especially medially, so that it is not certain that the remaining 60 to 73 per cent of the fibers of the pyramidal tract all arise outside area 4. Nonetheless, a fairly high proportion of them must have other origin.

That the pyramidal tract contains fibers deriving from parts of the cortex other than area 4 has long been recognized, but the questions are: how extensive an area, and where, and how many fibers? We now know that retrograde changes in cells, either chromatolysis or atrophy, are acceptable evidence of a positive relationship of cells examined to fibers damaged, but that the absence of visible changes does not prove that the cells examined had no connection with the fibers interrupted. Conclusions derived from the absence of chromatolysis are invalid. Considering positive

evidence only, Levin and Bradford (1938) found in the macaque monkey, in addition to the usual cell changes in area 4, unmistakable changes in areas 3, 1, 2, and 5 of the parietal lobe, following hemisection of the spinal cord, but they found no clear-cut changes anterior to area 4. They estimate that almost 20 per cent of the pyramidal tract may arise postcentrally.

Studies of fiber degeneration are fairly well in line with these cell studies. Speaking of the monkey, for which a great deal more is known than for the human, a parietal contribution to the corticospinal tract is now unquestionable. Minkowski (1924), Uesugi (1937), and Peele (1942a, b) have all described it, using Weigert or Marchi stain. Peele's studies give it a most extensive origin, from every parietal area, 3, 1, 2, 5, and 7. Fibers are most numerous from 3 and 7. Peele's novel and illuminating view of the possible function of these fibers will be considered later. Lassek (1942c), on the contrary, tends to minimize the parietal contribution; his largest combined pre- and postcentral ablation reduced the fibers of the pyramid by as much as 50 per cent, compared with 27 to 40 per cent after area 4 ablations.

Since the publication by Verhaart and Kennard (1940), revising Kennard's (1935) previous statements, there is now virtual unanimity of opinion that the cortex forward of area 4 contributes no medullated fibers to the corticospinal tract in the monkey. The studies of Hoff (1935) and of Hoff and Hoff (1934), made in the same laboratory, were apparently subject to the same error as Kennard's, and, if so, are subject to the same revision. The error consisted in misjudging the border between areas 4 and 6 (see Hines, 1936), in consequence of which the cortical ablations extended posteriorly into area 4. Prior work of Mettler (1935) and Levin (1936) had already established our present conception. As previously noted, retrograde cell changes have also not been detected forward of area 4 in the monkey. There are, as yet, no axis cylinder studies following cortical ablation of area 6, or 6 and 4, to indicate whether or not unmyelinated fibers leave area 6 via the pyramidal tracts.

Very little evidence is available for the human on contributions to the pyramidal tract from parts of the cortex other than area 4, even though cortical surgery must often have provided suitable material. Foerster (1923) gives the origin as pre- and postcentral, but quotes von Monakow as believing that the tract has a wider origin over the parietal lobe. There is no assurance that the human conforms with the monkey in the origin of the tract, and some reason why it should not. Since pyramidal function has clearly assumed a greater and greater role in total motor function in the course of primate evolution, it might be expected that the pyramidal tract would correspondingly extend its domain of origin. In man electrical stimu-

lation of the entire length of the precentral gyrus gives rise to discrete movements which are universally considered a function of the pyramidal tract. Yet in its lower reaches, at least, the Betz cell cortex is often buried in the central fissure (Putnam, 1940b). Foerster (1936b) has argued that such responses from what he refers to as area 6a∝ (but what is in this monograph called area 4a) are mediated transcortically to area 4, and executed through it. Foerster's statements on this point are not adequately documented Furthermore, his confusion of this area, in accordance with the maps of the Vogts, with area 6a∝ (see also pp 5 and 45 to 51) raises doubts as to the significance of his observations. In the one instance in which human material was examined for degenerating fibers following a premotor ablation (Minckler, Klemme, and Minckler, 1944), such fibers were found by Marchi method descending via the pyramid to the anterior white column of the same side of the spinal cord. Investigators of retrograde cell changes in area 6 following pyramidal lesions are not in agreement (Schröder, 1914; Wohlfahrt, 1932). Again, more and better evidence is needed.

As the evidence stands, areas 4, 3, 1, 2, 5, and 7 have been shown to contribute fibers to the pyramidal tract in the monkey, area 4, an indefinite portion of the parietal lobe, and probably area 6 in the human. No other portions of the cortex are currently even suspect of such contribution. Yet the largest of Lassek's (1942c) fronto-parietal ablations left 50 per cent of the fibers of the pyramid intact. What is the origin of these fibers? For the monkey, at least, it can be said with certainty that all fibers running lengthwise in the medullary pyramids are descending fibers (Tower, unpublished). Bodian's silver stain was applied to sections taken from above the decussation of the pyramids in a monkey in which the right pyramidal tract had been neatly severed at the trapezoid level 32 months before. The much atrophied right pyramid (shown grossly and in Weigert preparations, Tower, 1940) included the usual small bundles of transversely coursing internal arcuate fibers, which in the monkey swing down into the bed of the pyramids, but included no fibers, large or small, running lengthwise Moreover, none of these descending fibers is of infrapallial origin. When Mettler (1944) applied silver staining to sections of the medullae of monkeys surviving removal of all cerebral cortex, with and without removal of parts of the basal ganglia, he found no fibers remaining in the pyramids. Similar study by Lassek and Evans (1945) of the medullary pyramids from a human who survived virtually complete hemidecortication for 11 months, the insula only being spared, showed the transversely coursing arcuate fibers seen in the monkey, but only scattered fibers running longitudinally, "insignificant in number." And finally, a silver study by Marburg and Mettler (1943) of an anencephalic human (8 months gesta-

tion) in which the telencephalon was largely replaced by a cyst, with only small portions of neural tissue grossly identifiable, showed in the well-formed lower brain stem, no sign of the decussation of the pyramids or of the fibers of the pyramids, themselves.

Scant as this evidence is, and as yet not all adequately documented with detail and plates, it seems enough to prove that the pyramidal tract is constituted entirely of descending fibers, and almost as certainly that these fibers derive only from the cerebral cortex. Since only about 50 per cent of the pyramidal fibers can be accounted for at present as arising in the precentral region and the parietal lobes, a new search will have to be made for the cortical origin of the other 50 per cent. Cajal (1909) may have offered a lead in a description he gave of the manner of termination of certain large fibers of the pyramidal bundles within the pons (probably of the mouse) These large fibers, which presumably would be myelinated, bifurcate, he says, into large and small, coarse and fine fibers The large branches then terminate in pontine nuclei, whereas the small, and possibly unmyelinated fibers, continue their course with the pyramidal fascicle into the medulla oblongata. Such fibers, so far as our knowledge goes, might arise anywhere in the cortex where corticopontine fibers arise, in the frontal, parietal, occipital, or temporal lobes If unmyelinated, they would not have been detected in any fiber studies yet made, except Lassek's (1942c) on the parietal lobe This leaves unexplored possible temporal and occipital origin and frontal origin anterior to areas 4 and 6 It is unlikely that severing the fine fibers only, with the large branch intact, would induce retrograde cell changes, so only fiber studies may be applicable in a future attack on this problem.

Reconsidering the evidence it is now clear that a new outlook is required on the nature and potentialities of the pyramidal tract.[1] Certainly it is not the simple motor pathway from the large cells of the precentral gyrus to the cord that it was so long considered. Nor may "pyramidal" continue to be synonymous with "corticospinal." It is even possible that the tract may not be entirely motor. With the probability looming that a considerable proportion of the corticospinal fibers arises outside the main motor area, and some from parts of the cortex which exercise little or no known motor function, Peele's (1942b) suggestion that the component of corticospinal fibers from the parietal lobe might be considered, as others have considered the corticothalamic fibers, as a sensitization mechanism for cord sensory neurons, merits experimental investigation and serious consideration In the end it may be necessary to redefine the pyramidal tract.

[1] Walshe (1942) in a stimulating and critical review has already contributed to this

Course

The fibers descending from the cerebral cortex to the spinal cord in the corticospinal or pyramidal tract are nowhere found as a completely segregated bundle, but in the medullary pyramids the admixture of other fibers is minimal Some bundles of fibers of the arcuate systems usually cross the strand transversely, and various components of the corticobulbar system of fibers are present, depending on the level of the pyramid under consideration, but otherwise it is unadulterated, so far as is known. Above the pyramids, however, the corticospinal fibers are associated with other descending cortical systems bound for terminus in the brain stem. A rough estimate of the dilution of pyramidal fibers by nonpyramidal fibers may be obtained by comparing the cross section of the area ascribed to the pyramidal fascicle in the internal capsule and basis peduncle with the cross sectional area of the medullary pyramids. The dilution obviously diminishes with descent of the brain-stem, and very sharply in the passage through the pons. Fiber counts, however, would obviate the possible errors in this estimate stemming from changing fiber size and variable density of packing Descending fibers from cortical and subcortical levels intermingle in the cord, and mix generally with the proprius system of the cord, and to a lesser extent with ascending sensory systems So-called pyramidal lesions, when lodged either above the pyramids or in the cord, are, therefore, necessarily complicated by lesion of these other systems.

In their course through the brain-stem down to the pyramids, the pyramidal fibers are believed to give off collaterals, but inasmuch as the pyramidal fibers cannot be distinguished individually from the accompanying extrapyramidal fibers, it is not certain what fibers give off what collaterals until the corticospinal group becomes fairly condensed in its passage through the pons. Collaterals, suspected or described, pass off to the striatum, to the substantia nigra, and to the reticular formation of the upper brain-stem. The pontine collaterals are unquestioned and numerous Whether further collaterals are given off in the bulbar course of the tract is not clear. Cajal (1909), working with mice, describes or figures them in a number of places (pp. 913, 957), but states (p. 890) that the pyramidal fibers do not give off a single collateral in their bulbar course. Corticobulbar fibers, swinging out of the pyramids, must be distinguished from collaterals. Numerous anomalies have been described for the cat and man in the course of parts or the whole of the pyramidal tract, but these cannot be detailed here.

At the lower end of the medulla oblongata the pyramidal tract of each side breaks up into two or three groups of fibers, the largest of which decussate and pass into the lateral white columns of the opposite sides of the cord The degree of decussation is more variable in the human brain, ex-

amined grossly, than in the brains of other primates, or of cats. Flechsig (1876) found in his series of human brains some with large lateral and negligible anterior pyramidal tracts and others with large anterior and small, though never absent, lateral tracts. In one extreme case there was no gross decussation at all, although some lateral tract was detectable in sections; in another, there was apparent total decussation. Correlating with the first case, Zenner (1898) reported a case of hemiplegia in which both the lesion and the paralysis were on the left side, and in which, at autopsy, the pyramids appeared uncrossed.

Scattered observations by Marchi technique on human cords, after cortical or capsular lesion, indicate that the human usually possesses a large crossed lateral bundle, a small uncrossed lateral bundle, and an exceedingly variable uncrossed anterior bundle of pyramidal fibers. The last usually terminates in the cervical or thoracic region, whereas the first runs the length of the cord, as may the uncrossed lateral tract. The various bundles have been more thoroughly examined in the lower primates, and similar components found (Fulton and Sheehan, 1935).

Considerable attention has been devoted to a possible topographical arrangement of fibers within the pyramidal tract at different levels. Foerster (1936a) illustrates his work with a diagram of the cord arrangement; leg fibers, lateral or superficial; and arm fibers, medial or deep; but nowhere does he give the evidence supporting this concept. Those who have looked into the matter more thoroughly have concentrated on the brainstem, peduncles, and pyramids. Working on man, Brouwer (1917), Fischer (1905), Hoche (1900), and van Valkenburg (1913) all reported little or no evidence of such segregation at the level of the pyramid. In the monkey, Peele (1942b) found fibers of parietal origin scattered ventrolateral in the pyramid. Again in the monkey (Tower, unpublished work), a series of three carefully controlled partial sections of a medullary pyramid, one of the lateral half, one of the medial half, and one of the full width to half the depth, showed by the similarity of the functional defect in every case that fibers for each part of the opposite side of the body must be generally distributed through the pyramid. In the monkey, therefore, and in man, there appears to be no topographical arrangement of corticospinal fibers at the pyramid level. The possibility of segregation in the cord remains to be explored for both species.

Termination

The corticospinal fibers are generally believed to terminate in the deeper parts of the dorsal horn or the intermediate gray matter of the spinal cord. Marchi technique shows the fibers swinging into this region.

Rasdolsky (1923) applied a technique of light green-fuchsin staining, which, he asserts, will stain degenerating nerve fibers electively to their ends, and illustrated the termination of degenerating descending systems entirely in this region following motor cortex ablation or hemisection of the cord in dogs. This work needs confirmation. Hoff (1932, 1935) and Hoff and Hoff (1934) have applied Cajal's reduced silver method to the study of button terminals degenerating in consequence of cortical ablation in cats, monkeys, and chimpanzees. They found the degenerating terminals numerous not only on cells in the intermediate grey zone and at the base of the dorsal horn, but some also on ventral horn cells in all species. Degenerating buttons were found in all species on both sides of the cord, in both sites, from unilateral cortical lesions. They concluded that the usual terminal of the pyramidal tract fiber is on an internuncial neuron.

Summary

The pyramidal tract, as usually conceived, consists of the bulk of the nerve fibers making up the medullary pyramids. These fibers are, without exception, descending fibers, and almost certainly of cortical origin. They are corticospinal and corticobulbar fibers. Very nearly all the large fibers, and at least 50 per cent of all the fibers in the pyramids originate in the precentral region and the parietal lobe. This is the best known group of fibers in the pyramids. Where the remaining 50 per cent of fibers arises is not known. Through the decussation, most of the pyramidal tract is brought into relation with cells on the opposite side of the cord, and chiefly with internuncial neurons, not motor horn cells. Uncrossed bundles, however, pass in the lateral and ventral funiculi to the same side of the cord.

FUNCTION

Our first insight into the function of the pyramidal tracts came from considering hemiplegia in man. Türck's three papers (1850, 1851, and 1854) are a good example of the growth of understanding which resulted as soon as anatomical examination was coordinated with clinical observation. In the first paper Türck noted the crossed relationship between a capsular lesion (3 cases) and the resulting paralysis, but did not consider the fiber tracts involved. The second, and most important paper, described the course of the degenerating tract from the site of lesion, which in his now enlarged series of cases was sometimes cortical, sometimes capsular, and sometimes in the cord, through the brain-stem and cord. He applied the terms "Pyramiden-strang" and "Pyramiden-seiten-strang" to the respective parts. Türck postulated that this "strang" carries motor impulses.

but pointed out that the paralysis following its destruction is incomplete, and he considered the possible existence of other descending systems. In the third paper he added the observation that lesions in the caudate and lentiform nuclei which do not injure the internal capsule, and also small thalamic lesions, produce no alterations in the cord (judged, apparently, from fresh sections). Cortical lesions, he added, may or may not result in massive cord degeneration.

Hughlings Jackson's profound analysis of epileptiform and other neurological disorders contributed two concepts. The first was the concept of localized and somatotopically organized control of movement in the cerebral cortex. The second concept postulated a hierarchy of motor control in the neural axis ranging upward from most automatic–least voluntary to most voluntary–least automatic. As soon as the stimulating electrode was applied to the cerebral cortex by Fritsch and Hitzig (1870), the resulting demonstration of somatotopically organized foci for the control of movement at once confirmed Jackson's first postulate and opened the era of direct experimentation upon the cortical control of movement and upon the functions of the pyramidal tract.

In primates the foci from which muscular movements can be elicited by electrical stimulation of the pyramidal tract are disposed in dorso-medial–ventrolateral order, anterior to the central fissure. The most caudal representation is on the mesial surface of the hemisphere, and the face, tongue, etc. are most ventrolateral. A segmental arrangement is roughly followed, but Woolsey, Marshall, and Bard (1942), by minute examination, have found a significant departure from the accepted order in monkeys, a departure which corresponds with a more thoroughly analyzed departure from simple segmental arrangement in the postcentral sensory cortex.

For good reasons the human cortex is less thoroughly known by electrical stimulation than is that of the monkey or chimpanzee. In the first place the total picture must be put together from stimulation of a large number of individuals rather than from exhaustive stimulation of a few. In the second place, much of the Betz cell cortex is buried in the central fissure where it can be stimulated in an experimental animal without too great difficulty but where it has rarely been stimulated in man. Or, it lies on the mesial surface where it is also not easily accessible (Scarff, 1940).

The most intensive examinations of the movements resulting from electrical stimulation of the human cerebral cortex have been those made by Foerster (1936b) and by Penfield and Boldrey (1937). The latter is especially significant because it assembles and analyzes only results uncomplicated by epileptiform phenomena. Leyton and Sherrington (1917), Hines (1940), and Dusser de Barenne, Garol, and McCulloch (1941) have

done the most thorough work on the chimpanzee. Numerous investigators have worked with monkeys, but the work of the Vogts (1919) has perhaps been outstanding. No attempt will be made to analyze the detail of somatotopic organization in the cerebral cortex. It is too well known. All I wish to do is to call attention to some characteristics of the response.

With minimal current and without prior stimulation, the responses obtained from a given cortical point prove to be quite constant. The contraction may involve greater or lesser parts of single muscles or of muscle groups, but the result is always spoken of as a movement because of the orderliness which characterizes the whole. How well integrated the movement is, is a function of experimental conditions. In deep anaesthesia, when no tone is present in the musculature, contraction is the only possible result, and integration is therefore evident only in the location, timing, and extent of contraction. With anaesthesia light enough to permit sustained tonic innervation in the musculature, reciprocally integrated relaxation and contraction are always demonstrable. Hering and Sherrington (1897) were among the first to study this relationship, followed more thoroughly by Graham Brown and Sherrington (1912) and by Cooper and Denny-Brown (1927). The cortical foci are, however, by no means unmodifiable in their responses. Immediately precedent activity, either at the cortical level or in the spinal cord, may modify the unconditioned response, to reinforce it, weaken it, or reverse it completely. The paper of Graham Brown and Sherrington referred to is largely devoted to examining this instability of a cortical point. Although much of this lability may be expected to derive from the complexity of cortical organization, that is, to be intracortical, the fact that previous or concurrent activity at the segmental level may also modify the result of cortical action indicates that activity projected from the cortex is far from being predetermined. The single pyramidal fiber may, therefore, carry impulses capable of producing a variety of effects, depending on other factors. With partial pyramidal lesions such as are usual in man this may well be the basis for the frequent and remarkable recoveries of function.

After decades of unquestioned assumption, it would seem superfluous to prove that the topically organized control of movement exercised from the cerebral cortex is executed by the pyramidal tract. But when that assumption was put to the test, incidental to experiments for the study of nonpyramidal cortical action, it proved to be subject to some reservation. Severing one or both medullary pyramids, preferably both, eliminates corticospinal or pyramidal action from the related cortex, and all responses in neck, trunk, and extremities then obtained from the cortex are, by definition extrapyramidal. If the cortex is stimulated both before and after

severing the pyramids, the pyramidal contribution to the total response may be assayed. Proceeding in this manner with a large series of acute and chronic bilateral pyramidal sections in cats (Tower, 1936), and another series in monkeys (Tower and Hines, unpublished), the proof has been furnished that somatotopically organized control of discrete movement is a function of the pyramidal tract; it is completely eliminated from the cortex by section of the pyramid. This is confirmed by the functional loss in animals or men surviving such lesions. However, the extrapyramidal activity which is peculiar to area 4, and remains excitable after both pyramids are cut, is also organized somatotopically; but both the movements produced and the organization are on a large scale of distribution. The extrapyramidal activity characteristic of area 6 is not so organized. Not somatotopic organization primarily, but organization for discrete control of movement characterizes the cortical arrangements for pyramidal function. Stimulation of the human cortex after destruction of the pyramidal tract in the internal capsule has similarly shown (Foerster, 1936b) that discrete control of movement is abolished, without leaving any evidence of somatotopically organized extrapyramidal action. But a capsular lesion of extent sufficient to destroy the pyramidal tract must also destroy much of the extrapyramidal projection systems as well, certainly all those deriving from area 4. This being the case, the results of subsequent cortical stimulation cannot be interpreted, in their departures from the normal, as a measure solely of pyramidal function, any more than the disorder exhibited by the surviving individual can be considered a pure pyramidal defect. The spasticity attending capsular lesions, now recognized as an extrapyramidal symptom (Hines, 1937), is the clearest evidence of the error of such thinking.

The direct approach to the function of the pyramidal tracts by electrical stimulation of their cortical origin creates a picture somewhat like a keyboard upon which the more creative parts of the cortex, Hughlings Jackson's highest motor centers, may play Moreover, the unit of play, so to speak, is a discrete movement, combining contraction of some muscles and reciprocally related relaxation of other muscles. Whole muscles need not be involved, and parts of a number of muscles may participate in one movement. In general the muscles involved are located on the opposite side of the body, but not always. The significant cortical orientation is to the opposite side of the external world. And since movements with that vector may involve muscles located on the opposite side of the body, as is usual, or on the same side of the body, as is frequent with axial musculature, or on both sides, the cortex is provided with access through the pyramidal tract to the requisite muscles. The ipsilateral cortical control of the

sternocleidomastoid muscle is a case in point. Movements produced from
the cortex by electrical stimulation under conditions in which only the
pyramidal tract appears to be operating are by no means performances
useful to the individual, although the same is not true when extrapyram-
idal cortical action is brought into play (Tower, 1936). The responses
impress one as the raw materials of pyramidal function, not as the ade-
quate expression of that element in total motor function which is clearly
the basis for the remarkably delicate and various motor performances of
primates.

For insight into the way in which pyramidal function participates in
total motor function, and into the manner in which the higher levels of
motor organization use the keyboard of the precentral gyrus, we must
revert to indirect inquiry: observation, analysis, and interpretation of
the symptomatology of pyramidal lesion—the original mode of attack.
Only now we shall concentrate on the uncomplicated pyramidal lesion
resulting from severing one or both medullary pyramids, avoiding, except
for comparison, the combined pyramidal and extrapyramidal lesions which
are produced by destruction in the cerebral cortex, in the cerebral white
matter, internal capsule, basis pedunculi and pons, and the spinal cord
Inasmuch as lesions restricted, or even relatively restricted, to one or both
of the medullary pyramids are exceedingly rare in man, this analysis will
deal largely with controlled lesions deliberately produced in experimental
animals—cats, monkeys, and chimpanzees The results of these experi-
ments will be correlated, so far as possible, with what scattered and im-
perfectly studied human cases are available, possibly ten in all.

Severing the medullary pyramids is an experiment which has been
attempted repeatedly on a variety of animals. Rothmann (1902, 1904,
1907) tried it on monkeys and chimpanzees, and Schüller (1906) on
monkeys. My own work with pyramidal lesion in primates has been car-
ried out on a large series of mature and immature monkeys and a small
group of chimpanzees, and includes, besides a published study of 10 uni-
lateral lesions and 1 bilateral lesion in the adult monkey (Tower, 1940),
unpublished studies of pyramidal lesions in the infant monkey (3 uni-
lateral and 1 bilateral); partial pyramidal lesions in adult monkeys (3
deliberately incomplete and 3 accidentally so); combined pontine and
pyramidal lesions (Tower, 1942); combined tegmental and pyramid lesions
(unpublished); and in conjunction with Dr. Hines, a study, still incom-
plete, of cortical lesions superimposed on pyramidal lesions. With the
exception of two monkeys still surviving in the last study, all these lesions
have been verified histologically. Moreover, all the monkeys, with the
exception of one infant, survived operation from 3 weeks (when some were
killed for Marchi) up to 4 years.

The chimpanzee study, still unpublished, was made on four animals. Three of these had unilateral lesions, and of these one was killed after 2 years, and the others died 8 hours and 5 days after operation. The fourth animal had a very nearly complete bilateral pyramid section, and was killed 1 year and 8 months thereafter. All lesions were verified histologically.

Pyramidal lesion in the monkey and cat[2] produces a condition which is best characterized as a hypotonic paresis. There is no paralysis, in the sense that no member or part of a member is rendered useless, but there is a grave and general poverty of movement, and impairment of what usage remains. Both the hypotonia and the paresis are far graver in the monkey than in the cat.

The disorder of movement, or paresis, attacks movement or usage in proportion to its discriminative quality. All fine usage is eliminated. In this process some whole performances, such as the opposition of thumb and index finger (to pick up small food objects), individual movements of any digit, and elevation of one shoulder (to empty the food pouch of that side) are eliminated. The usage which survives, be it posture, progression, fighting, or reaching-grasping, is stripped of all the finer qualities which make for aim, precision, and modifiability in the course of execution. These remaining stereotyped performances are useful still, but they are by no means the skilled performances of the intact animal. Inasmuch as the residual performances may require the most intense voluntary attention for their successful employment, as happens after bilateral pyramidal lesion in the adult monkey (Tower, 1940), the condition cannot be called a complete voluntary paresis. In other words, extrapyramidal action from the cortex may be employed quite as voluntarily as pyramidal action. The selective destruction is of the least stereotyped, most discrete, movements or elements in movement.

The hypotonia of pyramidal lesions is generally but not equally distributed throughout the body musculature from the neck down. The defect is demonstrable as diminished resistance to passive motion of parts, or by direct palpation of the muscles. With a unilateral lesion, the hypotonia is graver in the extremities and abdomen than in the remainder of the axis, and in the monkey, graver in the leg than in the arm. A bilateral lesion extends the defect almost equally to the axial musculature without increasing the severity in the extremities, giving a measure of the functional significance of uncrossed pyramidal innervation and of its locus of action. Certain usage defects correspondingly make their appearance, most con-

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[2] A number of observers, most recently Liddell and Phillips (1944), disagree with the author concerning the results of this lesion in the cat

spicuously as inability to turn, elevate, or depress the head independently of the body, that is, to use the neck musculature discretely.

Superficial reflexes, such as local reactions to pin prick, and the abdominal and cremasteric reflexes are raised in threshold or abolished; the deep reflexes are correspondingly raised in threshold and become slow and full because they are unchecked by antagonistic contraction. The knee jerk is often pendular, as with cerebellar hypotonia. In the monkey the plantar reflex, which rarely takes the form of a Babinski response, is also raised in threshold but unaltered in pattern.

Of more special tests and performances, tonic neck reflexes have never been elicited. Contact and visual placing reactions are absent in the paretic extremities, and proprioceptive placing and hopping reactions are enfeebled and high in threshold. The ability to hold on to objects and to grasp is greatly weakened in the adult monkey, but nevertheless the stereotyped reaching-grasping act is one of his most useful performances. In circumstances in which strength is not much in demand, a conspicuous feature of this grasping activity is the animal's inability to terminate it at will, i.e., to open the hand and let go, especially so long as there is tension on the flexor tendons. With pyramidal lesions in infancy, which never produce as much hypotonia and general weakness as such lesions in the adult the grasp is stronger, and the inability to let go is a practical handicap in climbing, which the animal must circumvent.

With unilateral pyramidal lesions in the monkey, the hand and foot on the side affected by the lesion are conspicuously cooler than on the normal side, and enduringly so for years, except after violent exercise, or in an environmental temperature of 90 degrees F. or more, or during heating tests for vasodilator action. Analysis of this vasomotor disorder has shown (Tower, 1940) that it is probably compounded of a large deficit of tonic excitation operating from the cortex via the pyramidal tract on the cord dilator mechanism, and a much smaller and usually submerged similar tonic deficit in the constrictor mechanism. In consequence, the constrictor mechanism is relatively overactive, producing the continuously lower skin temperature, and vasomotor reflexes are sluggish and enfeebled. The enfeeblement of vasoconstrictor action is in evidence only as failure to check or to antagonize extreme vasodilator reactions, as after violent exercise, and on very hot days, or at the height of generalized reflex vasodilator reactions produced by heating parts of the body remote from those under observation. Such vasomotor disorders were not noted in the cat, the work on which preceded that on the monkey. If pyramidal lesion in the cat produced any difference in skin temperature of the two sides, the difference was insufficient to command attention.

Pyramidal lesion in the chimpanzee likewise produces a condition of hypotonic paresis, but unlike the monkey and cat, in which the hypotonia and the paresis are about equally striking, the paresis is outstanding and the hypotonia more obscure. The paresis eliminates, in the chimpanzee, the same discrete or non-stereotyped elements in usage which are eliminated in the monkey or cat, but in proportion, the total defect is greater as these elements bulk larger in the total usage of that species. Moreover, performances such as progression are much more weakened in their stereotyped basis in the chimpanzee than in the monkey, as though pyramidal function contributes more to their execution than in the lower animals. Placing, hopping, and dropping reactions are abolished to all forms of stimulation, not merely to contact. The difficulty of letting go, noted in the monkey, becomes, with the powerful development of the flexors of the hand and the slight structural flexion of the terminal phalanx in chimpanzees, an emphatic proprioceptive reflex grasp. So long as the flexor tendons are under tension, the animal is unable to open his hand. This presents the chimpanzee as he climbs or swings around his cage, with a problem which he solves, as does the young monkey, by learning to throw his weight up just enough to relieve the tension, whereupon he quickly disengages the hand. The chimpanzee, with his weaker toe musculature, has no difficulty with foot grasp.

Any examination of tone in an experimental animal is satisfactory only in proportion to the degree to which a standard condition for its examination can be established and maintained. In the cat and monkey a standard condition of passive uncooperativeness is fairly easily obtained. The chimpanzee, on the contrary, is extraordinarily unstable in mood, swinging from unmanageable uncooperativeness to equally unmanageable cooperativeness. And the tone in normal musculature varies correspondingly. With the normal side wholly relaxed, a common condition, the side affected by pyramidal lesion is generally found to be equally relaxed, and certainly no relative hypotonia then exists. But in the numerous and various conditions in which the extremities are tonically innervated, the paretic side usually opposes less resistance to passive motion than the normal. The hypotonia is most clearly in evidence in spontaneous activity. For example, in the animal's common habit of picking up the affected forearm by the good hand to place it in the lap, or in a more comfortable position, the dead weight and sagging muscle bellies of the paretic arm are unmistakable. Again, as the animal moves about a large cage, swinging from bar to bar, grasping alternately with each hand or foot, the paretic extremity swings like a flail, unchecked by tonic innervation, while a normal extremity is always visibly in tone.

The deep reflexes of the chimpanzee are altered surprisingly little by pyramidal lesion. They are easily obtained in the paretic side, usually more easily than on the normal side where they are hampered by the animal's attempts to cooperate. The reflexes are large in scope, though not pendular, not especially brisk or slow; they are neither definitely attended or unattended by check contraction in antagonists They do not radiate. When the chimpanzee is completely relaxed but mentally alert (not sleepy), deep reflexes of both sides have these characteristics about equally Clonus is not met with, either in normal or in paretic extremities. Nor have tonic neck reflexes ever been elicited.

Of the superficial reflexes, the abdominal reflex is abolished, and the local contraction to pin prick is everywhere raised in threshold. Since none of the successful pyramid sections were on male chimpanzees, I have no evidence on the cremasteric reflex. A Babinski response, that is, conversion of the normal plantar reflex from flexion and adduction of the big toe to extension and abduction with extension and fanning of the other toes, has been an immediate, invariable, lively, and enduring consequence of pyramidal lesion. Usually the response also includes dorsiflexion at the ankle, flexion and adduction at the hip, and sometimes at the knee. The amount of fanning has varied with the individual chimpanzee.

The chimpanzee with unilateral pyramidal lesion rarely shows the palpable difference in skin temperature between the hands and feet of the two sides which is so noticeable in the monkey. The use of the dermatherm (Tycos) following the procedure developed for the monkey, does, however, bring out some difference, and as in the monkey, the paretic hand and foot (especially the hand) are cooler. This difference has never been discernible in the first week of the operation, but it later becomes evident, increasing with the passage of months But even so, frequently no difference is detectable, or the paretic side is warmer, a condition which was met with only in very special circumstances in the monkey.

Both the chimpanzees and monkeys surviving unilateral pyramidal lesion for a sufficient time, begin to show after about two months a palpable, and later a measurable, difference in muscle bulk between the two sides, the paretic muscles bulking less. In growing animals this could be deficient development; in adult animals it is unquestionably atrophy. Histological examination of the muscle shows simple atrophy; the individual muscle fibers are small but intact. Contractures have never been detected after pyramidal lesion performed later than the first year of life, but all animals (monkeys only) in which this lesion was made in early infancy, have shown, when examined under profound nembutal anaesthesia a year or more later, muscle lengths shorter on the paretic than on

the control side. Bone development has been normal. Whether these shorter muscle lengths represent deficient development or contracture is largely a matter of definition of terms.

So far, no case in man of uncomplicated lesion of the medullary pyramids has even been studied and put on record; there is no case comparable with the lesions deliberately produced in animals. By combing the literature, ten possible cases have been found, all imperfect in one way or another. These have already been individually summarized (Tower, 1940). The most significant cases are those of Környey (1936), Davison (1937), and Hausman (1939); Davison's two cases with autopsies. Dr. Hausman has been good enough to furnish me with a much more complete report of his case than is yet published, with permission to use it. The individual is still alive.

Reviewing these reports again in the light of the work on the chimpanzee, the parallelism is striking. Flaccid paralysis characterizes the lesions in both. "Flail-like" is a term which Hausman employed for the condition of the extremities in his case, a term which inevitably comes to mind while watching the chimpanzee with a unilateral lesion swinging the paretic extremities through the air, but it is a term which never fits the monkey or cat. The deep reflexes are described variously as "very active," "gesteigert," or "increased," words which might almost be applied at times to the chimpanzee's unimpaired and unchecked deep reflexes. The abdominal reflex is absent. The plantar reflex is typically extensor, a Babinski sign. In long-standing cases the muscles are atrophied but show little or no contracture. Skin temperature is mentioned in only one case besides Hausman's, and that one is the most complicated by lesions elsewhere in the brain. In this instance the paretic hand was cooler. This silence probably indicates that in man as in the chimpanzee the vasomotor disorder following pyramidal lesion is not very great.

Hausman's case merits more detailed description. Besides the flaccid paralysis, the reflex changes, and atrophy without contracture characteristic of the lesion, he gives in his personal communication further significant facts. The loss of fine movements is strikingly like that described for the monkey and chimpanzee, but emphasized by the greater demands for such usage in the human. Moreover, this patient had difficulty in releasing the hand grip, which often could be overcome only by using the normal hand to open the fingers. Tonic neck reflexes were not elicited. Fanning of the toes attended the Babinski response. Skin temperatures, measured with a radiometer, were lower on the affected side of the body than on the normal, especially so on the hand and foot. While there is nothing in the record, no cranial nerve or other involvement to indicate the exact location

or nature of the lesion in this case, the parallels between the disorder exhibited by this patient and those met with after unilateral pyramidal lesion in monkeys and chimpanzees are so outstanding, far more than this brief summary covers, that I can only believe this represents the one case of unilateral pyramidal lesion (partial only) in man ever to be adequately studied. Until autopsy confirms this, however, we cannot be sure.

Obviously these cases, especially Hausman's, depart significantly from the usual clinical concept of the syndrome of pyramidal lesion in man. This could be summarized in the phrase "spastic paralysis." The paralysis is there, to be sure, attended by diminished or absent superficial reflexes and the sign of Babinski, but evidences of spasticity, such as exaggerated deep reflexes with clonus, contractures, and tonic neck reflexes are wanting. As has been pointed out before, the lesions in man which produce the usual hemiplegia, or spastic paralysis, whether they lie in the cerebral cortex, internal capsule, or cord, are inevitably mixed pyramidal and extrapyramidal lesions, destroying fiber systems in both categories. And the symptomatology might be expected to be correspondingly compounded. The pyramidal elements in the total are easily recognized: loss of discrete control of the skeletal musculature, muscular atrophy, impaired or abolished superficial reflexes, and the sign of Babinski. But the muscular contractures, tonic neck reflexes, and the phenomena of spasticity are additional disorders, the consequences of extrapyramidal destruction. Associated movements are seen with the medullary pyramidal lesion in the lower primates and with hemiplegia in man, and seem to represent, not spastic phenomena, but action of the surviving extrapyramidal mechanism as it is brought into play to compensate for the defect. The variability of the vasomotor defect with hemiplegia in man may result from various compounding of pyramidal and extrapyramidal factors, but this needs further investigation. Also the quantitatively much graver total motor defect of a complete hemiplegia in man, while it probably derives in large part from a greater pyramidal dominance in man, may well include additional destruction of cortical extrapyramidal motor functions which have also assumed increased importance with increasing total cortical dominance. What we know of extrapyramidal motor function in the cat, monkey, and chimpanzee gives clear indication of a trend in this direction.

Weighing all the evidence, the inquiry may now be made: what are the reliable signs of pyramidal lesion? In man and the chimpanzee unquestionably the sign of Babinski* when the fibers for the foot are involved. But speaking more generally, since the hypotonia of pyramidal lesion is so

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* For conditions other than lesion of these fibers in which a Babinski sign has been obtained see Lassek (1944)

easily obscured by the spasticity of auxiliary extrapyramidal involvement, therewith also altering the character of the deep reflexes, tone and the deep reflexes are unreliable indices, as is also vasomotor condition. In contrast, the superficial reflexes seem equally defective with any level of pyramidal involvement, and in that respect are reliable; but they are slim evidence. With an intact segmental motor mechanism, discrete control of movement is probably the one generally applicable and reliable test of pyramidal function. Although loss of this control is most conspicuous in the digits, tests are readily devisable which will demonstrate it in any part of the musculature. Thus the one unique function of the pyramidal tract, its minute control of the skeletal musculature, appears in default as the most reliable sign of pyramidal lesion, affording, moreover, a quantitative measure of the status of pyramidal function which may be topographically applied to all parts of the body.

Summary of Function

Reinterpreting the results both of cortical stimulation and of pyramidal lesion in the cat, monkey, chimpanzee, and, with reservations, man, the functions of the pyramidal tract appear to be characteristically organized both in space and in time. The spatial organization derives from a relatively stable topographical relationship between loci in the cortical field of origin of the tract and loci in the motor mechanism of the spinal cord. The fineness of this topographical organization underlies the unique feature of corticospinal function: the ability to bring into action any portion of the skeletal musculature, and in all combinations. This detailed control of the skeletal musculature makes possible the discrete usage of the musculature, especially of the digits, and the modulation of extrapyramidal activity, which are outstanding pyramidal functions. Furthermore, by increasing the excitation in specific portions of the segmental mechanism, fragments of the stereotyped patterns of extrapyramidal activity can be brought to threshold as part reactions, detached from the frame which usually gives them usefulness. The pyramidal tract operates in a crossed relationship on the extremities, but bilaterally on the axial musculature other than abdominal.

The functions of the pyramidal tract are, however, not covered by description, no matter how detailed, of results of stimulation in its field of origin, because the organization in time is not brought out in this manner. In time, the pyramidal tract operates in two phases. As a groundwork there is a tonic function, continuously in operation in the waking state, diminishing with somnolence and sleep. This may be viewed as a continu-

ous contribution to the central excitatory state of the segmental motor mechanism which facilitates and reinforces whatever action may be instituted at that level by incoming segmental or suprasegmental excitation. Its most notable effects are to reinforce muscle tone, to keep the thresholds of superficial and deep reflexes low, and probably to speed initiation of and facilitate more complicated action. This tonic function has been pictured by Adrian and Moruzzi (1939) in the impulses which may be led off from the pyramidal tract in the anaesthetized cat as persistent and spontaneous activity corresponding closely with the potential waves in the motor cortex.

Superimposed upon the tonic function is a phasic or episodic function, which appears as a specific contribution to individual acts or performances, and often as the entire performance. This enters into all somatic motor activity of any complexity to initiate it or to speed initiation, to confer on it adjustability in space, which is aim, and modifiability in time or in the course of execution. It contributes the elements of precision, lability, and finish to stereotyped performances. And more than this, in primates it makes possible all the finer varieties of usage, such as minute operations with the digits. It is in this function that discrete control of the skeletal musculature is most in evidence.

The tonic function provides a basis for rapid and strong action which the phasic function initiates, controls, and modifies. In the realm of somatic motor function this is all primarily excitation. There is no evidence of specific or primary inhibitory function as such beyond that entailed in the reciprocally integrated operation of excitation and inhibition in the segmental motor mechanism.

In all species studied the outstanding pyramidal function is the exercise of discrete control of the musculature in phasic action. Moreover, the pyramidal tract has full responsibility for this in all the species, although the volume and detail of that control increase enormously from cat to man. The tonic function is much in evidence in the monkey, and less so in the cat, though not out of proportion to the generally lesser importance of pyramidal function in that species. In the chimpanzee the phasic function is outstanding and the tonic function comparatively obscure. How the balance of these two is struck in man is hazardous to judge, but from Hausman's description that the resistance to passive movement is greatly diminished, the tonic function would appear to be at least as active as in the chimpanzee, and probably more so. That the phasic function is overwhelmingly more developed and more important in man than in the lower species seems unquestionable, even though no certainly complete human pyramidal lesions have yet been available to prove the point. Altogether, in the realm of somatic motor control the course of develop-

ment appears to involve an increase in the share of pyramidal action in total motor function, and a differentiation of pyramidal action in the direction of increasing discreteness of control. Moreover, there is a redistribution of weight of pyramidal control, tending away from the predominantly flexor action characteristic of the cat, through relatively balanced control in the macaque, to predominantly extensor control in the apes and man. This general tendency, which is subject to many specific reservations, probably is the setting for the development of the Babinski response with pyramidal lesions in the apes and man, and not in the cat and monkey.

In the realm of autonomic control, the pyramidal tract appears in the monkey to exercise a continuous or tonic influence on the vasomotor mechanism, largely as tonic reinforcement of vasodilator tone and reflexes Whether or not there is a further phasic action is uncertain. Such influence was not sufficiently outstanding to attract attention in the cat. In the chimpanzee either the pyramidal tract exercises only a feeble control of the cord vasomotor mechanism, or its control is so neatly balanced between vasodilator and vasoconstrictor influences, and between excitation and inhibition, that the abolition of the whole is without much consequence. Vasomotor disorder has not been an outstanding feature of the reports of possible pyramidal lesion in man, though Hausman found it. From this general silence it seems probable that the human pyramidal tract, like that of the chimpanzee, exercises either a feeble vasomotor control, or a control so balanced that its total elimination produces no outstanding results. Other possible autonomic effects have not been adequately examined.

The phasic function of the pyramidal tract, in so far as it employs discrete control of the skeletal musculature, certainly represents action from the keyboard of the precentral gyrus The best known fiber component and the best known function therefore go together. It is probably that the small component of very large fibers, the 2 to 3 per cent which probably derive from Betz cells, are most concerned with this fine usage of the musculature, especially when rapid initiation of movement and rapid cessation are involved. The tonic function and autonomic control might very well be taken care of by the fine fiber component of the pyramidal tract, and perhaps in part by components deriving elsewhere than from the precentral keyboard. The one attempt which has been made to evaluate the functional significance of the postcentral component of pyramidal fibers (Tower, 1940) was not rewarded; but certain limitations on the experiment were there pointed out. In fact, a whole new approach along the line suggested by Peele (1942b) may be in order. It is readily conceivable that a mechanism which operates as a sensitization mechanism for cord sensory neurons might on the one hand facilitate sensory projection cephalward, and on the other,

reinforce sensory operation on the segmental reflex mechanism, thus supporting muscle tone and other local reflexes. Certainly in the clinical literature hypotonia has been more frequently described as a consequence of postcentral than of precentral lesions (see Head, 1918, for man; Kennard and Kessler, 1940, for the monkey). In fact, exaggerated deep reflexes and hypotonia seem to attend such lesions, recalling the full reflexes and hypotonia of medullary pyramidal lesion.

Vasomotor control from the cerebral cortex is much too confused a subject to be analyzed here, particularly as species difference enters more largely into this than into any other pyramidal function. Nevertheless an unfinished study (Tower and Hines) of the balance of pyramidal and extrapyramidal factors in the cortical control of this function has shown that both the pre- and the postcentral cortices share it in the monkey. Again this offers possible scope for function of the obscure component of small pyramidal fibers.

The foregoing discussion is offered as suggestive only. It does not exhaust the numerous leads already present in the literature for function of components in the pyramidal tract other than the well known precentral component. It is intended primarily to complement the formulation in the first part of this study of the need for a revised and enlarged view of the anatomical constitution of the pyramidal tract by indicating a similar need for an enlarged view of its functions. When both these concepts are sufficiently mature, we may expect to find the totality of the fiber components of the tract fully engaged with known functions.

Chapter VII

ON EXCITATORY AND INHIBITORY PROCESSES WITHIN THE MOTOR CENTERS OF THE BRAIN

N. Bubnoff

and

R. Heidenhain

(Translated by G. v. Bonin and W. S. McCulloch)

OUTLINE OF CHAPTER VII

Excitatory and Inhibitory Processes

EXCITATORY AND INHIBITORY PROCESSES[1]

WHAT WE SHALL have to say is only a modest beginning of new knowledge, more apt to make us realize our ignorance about cerebral processes than to dispel it. Whoever has the temerity to utter definite opinions about problems so little known and so intricate should realize that his opinions can have no more than passing validity, and that the more quickly a body of known facts accumulates, the more surely they are replaced by other theories. Nonetheless, it is necessary for the development of science that at every step beyond the mere collection of facts an attempt be made to establish causal relations. Even if future progress should prove such attempts to have been misdirected, they would not have been made in vain.

I. ARE THERE CORTICAL MOTOR CENTERS?

Goal and Method of Investigation

After Fritsch and Hitzig had shown that electrical stimulation of certain small delimited parts of the cerebral cortex leads to movements of certain delimited groups of somatic muscles, an exceedingly voluminous literature sprang up, without, so far, leading to unanimity among investigators as to the significance of this fact. The pertinent observations are of two kinds: stimulation and extirpation. The latter, which has been performed frequently and extensively, was used only sporadically by us, not

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[1] Translated from N. Bubnoff and R. Heidenhain, Ueber Erregungs- und Hemmungs-vorgänge innerhalb der motorischen Hirncentren, Arch f d ges Physiol 1881, 26 137-200 The German original contains an introductory and a concluding paragraph discussing phenomena of hypnosis These paragraphs have been omitted The text was further shortened by deleting some repetitions and summaries Also the references contained in the original have been withheld

Rudolf Peter Heinrich Heidenhain was born in 1834 and died in 1897 He studied under Du Bois-Reymond, was later Professor of Physiology at the University of Breslau, and is best known for his work on secretion and resorption and the formation of lymph In 1880 he published a paper entitled *Der sogenannte thierische Magnetismus*

Nikolai Aleksandrovich Bubnoff was born in 1851 and died on December 18, 1884 An obituary in the form of a letter to the Russian Medical Society was published by the President of that Society, S Botkin, and was kindly translated and summarized by Dr George Boris Hassin "Bubnoff graduated from what is now known as the Military Medical Academy of St Petersburg and became an assistant to Professor Botkin (internal medicine) and began investigations on the physiologic action of *Adonis vernalis* on the heart Before finishing his work he entered the service in the Russian Army during the Russo-Turkish War of 1877, and was attached to the Red Cross where he worked under Pirogoff He contracted typhus and relapsing fever but recovered and returned in St Petersburg, where he resumed his investigations on *Adonis vernalis* He was sent abroad by the government to do investigative work under Heidenhain (in Breslau) On his return to Russia he served for a short time as regimental physician in a small frontier town, and then returned to St Petersburg to become Botkin's assistant"

because we did not realize its importance but merely because this widely used method did not seem to stand in need of further corroboration Doubts have arisen about the usefulness of stimulations and about the possibility of drawing from them stringent conclusions as to the motor function of the cortex, especially since L. Hermann (1875) emphasized that the motor reactions which can be obtained by the stimulation of certain cortical points are similar to those which can be obtained by the stimulation of subjacent tracts of white matter after the cortex has been removed. One could not be sure, therefore, whether the motor responses evoked by electrical currents through electrodes applied to the surface of the brain have their origin in the cortex or are due to spreading currents traversing the underlying white matter.

When two electrodes are put on the surface of a moist, conducting body, currents unquestionably traverse the entire body. It is hardly necessary to prove this by special experiments on the brain. It is equally beyond doubt that stimulation of both motor center and the fibers emerging from it must lead to effects in the same muscles. This makes it difficult but not impossible to decide whether the gray substance is excitable. For similarity of reaction is not identity. If differences in the mode of reaction of the cortex and of the subjacent white matter could be demonstrated, a proof would have been given for the independent role of the cortex in evoking movements when stimulated.

A large part of our investigations was planned to answer the question whether the responses to stimulation of white and of gray matter were similar or dissimilar. For that purpose it was necessary to know the form and the temporal sequence of the muscular contractions evoked by stimulation of cortex and of white matter. The contraction of a stimulated muscle had to be registered graphically, and the duration between the moment of stimulation and the moment when the muscle began to contract had to be measured. This duration we shall call "reaction time." The first goal of our investigation was to work out the conditions of excitability of the cortex as well as of the subcortical conducting fibers and intercalated ganglion cells, and to describe the temporal sequence of the process of stimulation and of muscular contraction. However, several unexpected phenomena so attracted our attention as to require elaboration. Soon these came to the forefront.

Experimental Animals—For almost all our experiments we employed morphinized dogs, a 2% solution of morphine hydrochloride was injected into the anterior facial vein We rarely used more than 8 to 16 centigrams depending upon the size of the animal Whoever has had a broad experience will know that the same doses in animals of the same size may have very different effects In a number of cases the alkaloid produces a sleep of many hours during which the animals, if undisturbed, lie completely motionless (state 1) The sleep may be more or less profound—a topic to be discussed later in greater detail In other cases a peculiar state of heightened

reflex irritability prevails Although the animals generally lie quietly, they startle in response to even the slightest sensible stimulus, particularly to sudden noises, to relapse very soon again into quiescence (state 2) State 2 cannot be transformed into state 1, no matter how great be the doses of morphine given subsequently It is easy on the other hand, to abolish state 2 by means of chloroform or, still better by means of chloral hydrate We have frequently done this for certain purposes Between the two states there are, of course intermediate ones

Preparatory Operations—After narcosis had been accomplished the left central motor region was exposed After removal of the bone and reflexion of the dura mater, one finds in a number of cases a more or less anemic brain—sometimes so anemic that it does not even fill the cavity of the skull In that condition of the brain narcotic sleep is generally deepest In other cases the brain appears decidedly hyperemic The greater the degree of hyperemia the greater is the danger that stimulation of the cortex will promptly elicit disturbing epileptic fits

In order to prevent cooling and other insults to the exposed brain the skin was first replaced Then the animal was put on its back and the right elbow exposed by a small incision A small transverse hole was drilled through the olecranon, an iron wire was threaded through the hole and the bone firmly attached to the operating board in such a way that the forearm stood vertically to the board and formed an acute angle with the upper arm To fix the forearm further, plaster of paris was put around the fore and upper arm from wrist to shoulder Since the plaster of paris when set, does not adhere very well to the surface of the operating board, an iron hook was let into the board close to the forearm before the plaster of paris was applied Hook and forearm were both embedded in the plaster Thus the extremity was sufficiently fixed so that the activity of its muscles could be measured

In all our experiments we have used the long extensor digitorum communis muscle Its tendon was exposed from the middle of the back of the hand up to the lower end of the forearm At the distal end a strong thread was tied around the tendon which was then cut distal to the thread The other end of the thread was armed with a hook to connect it with the recording apparatus to be described later In order to

prevent interference, the tendon of the extensor carpi radialis, which runs obliquely over the tendon of the extensor digitorum communis, was severed

Recording the Muscular Curve; Measuring the Reaction Time—The muscular curve was recorded by Baltzar's kymograph with automatic lowering of the drum used at maximum speed of rotation As a recording device, a Marey's tambour was used, connected in the usual manner by means of a rubber hose with a receiving tambour The lever of the receiving tambour was connected from below with the tendon of the muscle being used and from above with a brass coil spring by means of which a moderate extension was imparted to the muscle

We were not satisfied with recording the muscular curve to determine the beginning of the curve Firstly, it is difficult to record the beginning of the curve with absolute accuracy, particularly when the curve ascends gradually Secondly, the recording lever of the recording tambour evidently does not begin to move synchronously with the lever of the receiving tambour but has a lag proportional to the length of the rubber hose connecting the two tambours We overcame both difficulties by putting a platinum contact on the lever of the receiving tambour which could be adjusted so exactly as to break the current at the slightest contraction of the muscle, a contraction that was hardly noticeable at the recording lever The adjustment had to be made with great care and frequent readjustments were necessary, since during the course of the experiments the length of the resting muscle underwent slight alterations as a consequence of tonic changes The platinum contact was in series with a small electromagnet which recorded on the kymograph the opening of the contact at the beginning of the muscular contraction

This electromagnet was the lowest of three similar marking devices whose writing points were aligned vertically The uppermost one reacted on the opening of another platinum contact which marked the moment when the electric current was applied to the brain—ie, the beginning of stimulation The middle electromagnet recorded the vibrations of a chronographic tuning fork of 100 vibrations per second activated shortly before stimulation began Graphic representations like fig 65 were thus obtained

On the line 1—1, the muscle curve is recorded, on the line 2—2, the point α signifies the moment of stimulation, on the line
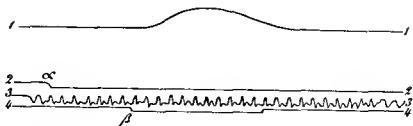
Fig 65

3—3, the vibrations of the tuning fork are registered, on the line 4—4, the beginning of the muscle contraction is recorded (at β)

Stimulating Device—The stimulus should influence the surface of the brain at precisely that moment which is given by α in line 2—2 This, of course, is possible only when stimulation takes place at an exactly definable moment What follows will show that this statement, which may seem self-evident, is by no means superfluous

One would naturally have used the current induced by breaking the primary circuit, since this would have fulfilled the requirements just stated We have indeed made a few experiments with a platinum contact in series with the uppermost of the three electromagnets and an inductorium When the contact was opened by the drop of a hammer, an induced current flowed synchronously with its recording by the kymograph

However, we soon had to give up this procedure, for muscular contraction can be evoked by a single impulse to the surface of the brain only with uncertainty and only when currents of enormous intensity are used Under such circumstances one has no way of knowing whether the cortex is stimulated directly or whether other distant parts are influenced by spreading currents On the other hand if we send tetanizing currents from an electromagnetic generator, currents so weak that they could hardly be felt on the tongue suffice to evoke motor effects However, such a series of impulses impinging upon the brain in themselves too weak to produce any effect, change, nonetheless, that part of the brain to which they are

applied and consequently render subsequent impulses effective It is impossible to determine the moment of the first effective impulse, but it is later, at any rate, than the instant when the tetanizing impulses begin to pour into the brain Therefore, if the latter moment is recorded on the rotating kymograph the reaction time will be exaggerated, since the actual stimulation can occur only an indefinite time after the instant of the supposed signal of stimulation

On account of the difficulties engendered by the use of induced currents, we turned to opening and closing of direct currents Ten to twelve small Grove's (circa 16 to 23 volts)[*]—the number has to be as high as that on account of the rather large resistance of our unpolarizable electrodes, which we shall describe later—delivered the current to a variable resistor which was connected in series with the uppermost of the three platinum contacts were opened (stimulation by positive wave, or by closing) and disappeared when the two contacts were closed (stimulation by negative wave, or by opening) To our amazement we found invariably that (1) the negative wave (closing of platinum contacts) produced muscular contractions at considerably lower intensities than the positive wave (opening of platinum contacts), (2) that the reaction time when stimulating by a negative wave was by 0 01–0 02 sec longer than when stimulating by a positive wave These results contradicted all the rest of our experiences, for when we compared the effects of positive or negative waves with each

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[*] Throughout this chapter the translators have inserted the voltage according to data given in the 19th edition of the Handbook of Chemistry and Physics, edited by Ch Hodgman, Chemical Rubber Company, Cleveland, Ohio

Fig 66—Diagrammatic sketch of stimulating device used by Bubnoff and Heidenhain
For description, see text

other by gradually increasing the intensities of the currents, it was regularly found that higher contractions were accompanied by shorter reaction times

This apparent paradox was eventually solved by discovering an experimental error It was found that on closing the platinum contact the current through the brain was not simply shut off but that multiple waves were evoked because the contact point tattled on the base plate The effect of stimulation was therefore not due to the first impulse but to successive waves, hence the greater contraction and, in spite of it, the apparent increase in duration of the reaction time

This error was not prevented with certainty by using a mercury contact, for when the platinum needle dives into the mercury the latter may easily be split about and thereby retard the definite establishment of contact. The following arrangement was finally used: The wire from the variable resistor to the contact in connection with the drop hammer was interrupted by an-

other platinum contact The experiment was then conducted in the following manner (fig 66) The hammer H, released mechanically by the right hand of an assistant, opened exactly simultaneously the contact S in the circuit of the signalling magnet S' and the contact R, in parallel with the current from the variable resistor P to the electrodes EE Thus the current entered the brain and gave the signal on the kymograph at exactly the same moment Immediately after the hammer had been dropped, the same assistant opened with his left hand the contact C and thereby interrupted the current through the brain This latter current, therefore, flowed only for a fraction of a second While the contact C was still open, the hammer was lifted and the subsidiary contact R thereby was again rendered effective Only then the contact C was closed again We stimulated the brain, therefore, by a constant current of a very short duration. Both making and breaking of this circuit was done by opening of platinum contacts In this way a positive

wave worked without exception with a much weaker current than a negative wave If by increasing the currents greatly, the negative wave became effective, the height of the contraction elicited by the positive wave was still greater This could easily be recognized by the shape of the curve registering the muscular contraction Only when the experiment lasted a very long time and when very strong currents were used, did it happen now and then that the positive wave had no effect and only the negative wave elicited contraction But then the conditions of excitability were changed so much that measurements appeared to be no more feasible

It is essential to use nonpolarizable electrodes, in spite of the fact that our predecessors unanimously dispensed with them Metal electrodes lead to the worst complications Quite apart from the rapid diminution of the current, due to polarization and to electrolytic disintegration on the surface of the brain at the points of contact, these electrodes lead by their polarizing action to gross errors in the measurement of the reaction time For the benefit of our successors, this has to be discussed in detail Prior to adopting as definitive the arrangement just described, we used a capillary contact worked by an electromagnet, sometimes to close the electrode circuit directly, sometimes in parallel with it In the first case the current was supplied to the brain by closing a contact of platinum in mercury, in the second case by breaking such a contact With the same resistance, the muscular contraction was higher and the reaction time was regularly shorter in the second than in the first case Since this difference completely vanished when nonpolarizable electrodes were used, it must have been due to polarization For when the electrode circuit is closed directly, the polarization occurring at the point of contact between metal and brain has no opportunity to dissipate when the current disappears after breaking the circuit When, however, the platinum contact is in parallel and the current disappears from the brain by closing of that contact, then polarization by conduction can be dispersed through this very current in series If polarization has not disappeared, then the next impulse impinging on the brain will rise less steeply and to lesser height than when polarization has disappeared, hence the greater effect of contact in parallel

But polarization has still more dangerous aspects When in our definitive arrangement (see above) metal electrodes were used, it happened not infrequently that after opening contact C and closing R which had been opened previously, an unexpected muscular contraction occurred This contraction disappeared when nonpolarizable electrodes were used This gave the explanation the contraction was simply due to a compensating polarization current flowing when the contact R was closed

After many experiments the most suitable form of nonpolarizable electrodes was found to be the following Zinc wire is hammered flat, amalgamated, and armed at one end with a cork By means of the cork this end is then put into a narrow glass tube which is shaped at its end like a writing pen The tube from which the zinc wire protrudes for a considerable distance is then filled with modeling clay worked with a saturated solution of zinc sulphate in such a manner that a clay cylinder surrounds the wire from all sides Into the free end of the clay cylinder a woolen thread saturated with a 1% solution of NaCl is put in such a way that thread and zinc wire are separated from each other by a broad layer of clay The thread has to be freed from superfluous salt solution by slight squeezing, since the clay avidly absorbs the salt solution and thereby become soft and smeary Two such small clay tubes, fastened close to each other in a suitable holder and armed with woolen threads about 8-10 mm long, represent very usable electrodes Apart from avoiding polarization, they have the great advantage that the threads applied to the surface of the brain at a small distance from each other can follow the pulsating and respiratory movements of the brain without becoming dislocated, thus avoiding many difficulties arising when stiff metal electrodes are used

Release and Recording of the Tuning Fork

—We have mentioned that time was recorded by an electromagnet and a tuning fork of 100 vibrations per second Shortly before stimulating, the tuning fork G (see fig 66) was activated in the following manner Both arms were kept attracted between the poles p and p' of a powerful electromagnet The circuit of the electromagnet was interrupted by a switch consisting of two cups filled with mercury (q and q') into which was dipped a copper fork k fastened to the axis A of the drop hammer H in such a manner that the fork was lifted out of the cups when the hammer

dropped, clearing the mercury immediately before the hammer opened the contacts *R* and *S*. The tuning fork, therefore, began to vibrate shortly before the stimulation of the brain was being recorded. By means of the vibration of the tuning fork, the current to an electromagnet was alternately opened and closed in a well-known manner.

Results

Position of Cortical Center for the Anterior Extremity—The experiments of Fritsch and Hitzig have acquainted us sufficiently with the region in which the motor center for the anterior extremity is to be sought. It is situated a little in front or behind the lateral end of the cruciate sulcus. However, one cannot hope to find with schematic regularity that picture of the cerebral convolutions which Fritsch and Hitzig have drawn. The cruciate sulcus varies in length and conformation, a fact which, incidentally, Fritsch and Hitzig indicate on the two sides of their figure. Consequently, one frequently has to search this region with the electrodes to find the excitable locus. In so doing, the intensity of the current has, of course, to be increased gradually. Once one has become acquainted with the great variety of external configurations, one finds the desired points quite quickly, even in a brain of unusual pattern. On stepping up the intensity of the current one generally notices, first, adduction and abduction of the paw and only later, activity of the extensor of the toes.

Amplitude and Course of Excitation in Medium Grades of Morphine Narcosis (State 1)—The animals are sleeping deeply and quietly. Reflex movements are not difficult to elicit, yet the reflex excitability is not noticeably increased. The contraction of the m. extensor digitorum communis longus elicited by cortical stimulation results in the curve drawn in fig. 67, 1. This is similar to the curve produced by the gastrocnemius of the frog, having a rapidly ascending and a slowly descending branch. In certain narcotic states—to be discussed later—the curve takes on the shape of fig. 67, 2.

M. Schiff states that the time elapsing between the moment of stimulation of the center of the posterior extremity and the beginning of the contraction of the gastrocnemius muscle is 7 to 11 times longer than it would be if the pathway from the center to the muscle were occupied by a homogeneous nerve fiber having the conduction rate of the sciatic nerve. It is this tardy onset of the contraction which causes him to assume that the electric stimulation of the cortex does not affect a motor but a sensory apparatus, the stimulation of which elicits first a sensation of contraction and only secondarily a movement. Franck and Pitres, who determined the reaction time in the same species that we used, found this time much longer when stimulating the cortex than when stimulating the subcortical white matter. In a published example, they found it in the first instance

equal to 0 065 sec., and in the second instance equal to 0.045 sec —a difference of fully one-third. This observation, which we are able to confirm, under conditions specified later, is of great importance, since it is of decisive value for the problem of excitability of the cortex proper It is impossible, however, to reduce the whole of our observations to such a simple statement as these scientists used to communicate the results of their measurements: "Chez un même animal"—so they say—"que l'excitation soit forte ou faible, unique ou multiple, la durée du la réaction time) est toujours identique, bien entendu pour une distance égale du centre excité." In different dogs the reaction time is said to differ only as the length of the pathway through which the excitation runs, and to vary within the limits of 0 05 and 0.11 sec. for the center of the anterior extremity and the common long extensor of the toes. In its simplicity this statement sounds fascinating, but when scrutinized more closely it shows inherent signs of improbability. For it is to be remembered that the reaction time in stimulations of the cortex is the sum of the following times: (1) The latent time of the stimulated elements of the cortex—i.e.,
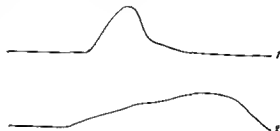
Fig 67

the duration elapsing between the moment of action of the electric current and the moment of the excitation generated in the elements of the cortex. (2) The conduction time from the cortex to the muscle, which is distributed between (a) the pathway through the conducting (central and peripheral) nerve fibers; (b) the way through the intercalated ganglion cells (3) The latent time of the muscle.

There is no doubt that in dogs of different sizes the first and third duration will be the same under otherwise identical conditions. The anatomical details within the central organ—i.e., the number of intercalated ganglion cells—will also be identical. The only difference, therefore, between animals of different sizes is a different length of the conduction pathway in the (central and peripheral) nerve fibers Now within nerve fibers a duration of 0 01 sec. corresponds to a length of 300 millimeters, but if a large dog should have a reaction time of 0.06 sec. longer than a smaller one, then the pathway from cortex to muscle should be 1.8 meters longer for the former than for the latter—a figure far beyond the difference in size obtaining between different animals. We realize fully, of course, that our calculations contain uncertain elements: for instance, the assumption that the rate of conduction in central and peripheral nerve fibers is the same.

The French authors worked with non-narcotized animals while we used almost exclusively morphinized animals. However, we performed two experiments on unnarcotized animals without obtaining results different from those obtained under morphine narcosis. All our observations, therefore, leave no doubt that within certain limits *the reaction time decreases when the intensity of stimulation increases, and vice versa.*

This rule is only too frequently overshadowed by the fact that the excitability of the central motor apparatus undergoes extraordinary variations, especially when the animals are incompletely narcotized. Conditions discussed later, whose effect hitherto could not even be suspected, then become effective. However, every series of observations uncomplicated by such changes in excitability confirms the rule stated above. Since the amount of excitation depends both on the intensity of the stimulus and on the degree of excitability, these two factors have to be discussed in detail.

The Intensity of Stimulus If the intensity of the current increases above the amount corresponding to a minimal muscular contraction, the height of the contraction increases and the reaction time decreases.

Examples Dog of medium size, injection of 12 cgm morphium hydrochloratum Deep narcosis—constant chain of 10 small Grove's elements (16-19 volts)—single stimulations at intervals of several seconds

Series	Variable Resistor	Reaction Time (in 0.01 sec)	Height of Contraction (in mm)
I	2000	5 0	4 5
	2200	4 5	11 0
	2400	4 0	16 5
	2600	4 0	18 0
	3000	3 5	25 0
II	1400	4 75	1 0
	1600	4 5	4 5
	1800	3 0	2 8(?)
III	1220	5 5	0 5
	1240	4 25	2 5
	1260	3 75	15 5

The figures of these three series clearly prove the rule just formulated. It is of advantage in such experiments not to choose too many steps of intensity because the excitability of the cortex is rapidly altered by oft-repeated stimulation.

Summation of Stimuli If one stimulates repeatedly at short intervals with that intensity which corresponds to a minimum contraction, the height of the contraction gradually increases to its maximum. Each preceding stimulus, therefore, leaves an after-effect which increases the effect of the following one

This summation of stimuli deserves a more intense study than has so far been accorded it. Our observations have not been carried out sufficiently for a systematic study of this question. As far as they go, however, they justify the following remarks.

(1) Single stimuli, ineffective in themselves, can become effective when repeated sufficiently rapidly. If the intensity of the current is much below its threshold value, as defined by a minimal contraction, a very large number of repeated stimuli may be necessary before contraction appears. In our earlier protocols (in the summer of 1880) there are many cases in which 20-odd, some in which 50-odd, and one case in which 106 repetitions were necessary in order finally to evoke a contraction.

(2) The shorter the interval between stimulations the more easily summation occurs. Intensities which did not lead to summation at intervals of 3 seconds were capable of summation when the interval was reduced to one second.

(3) Not only electrical stimuli leave an after-effect in favor of a subsequent excitation, but also any other stimuli which produce a contraction. If a reflex contraction is elicited in any way whatever, or if the animal spontaneously contracts the muscle used for the experiment, the electrical stimulus previously ineffective or weakly effective will immediately afterwards be somewhat more effective.

This is one of the reasons why all experiments are much more irregular in incomplete narcosis in which spontaneous movements frequently occur than in deep morphinization.

If, with constant intensity of stimulation, the height of contraction increases as a consequence of summation, the reaction time decreases correspondingly.

Example Medium-sized dog, 12 cgm hydrochloric morphine (after 0.3 gm chloral), 12 Grove's elements (19 to 23 volts), variable resistance, 2000

Stimulus Number	Reaction Time (in 0.01 sec.)	Height of Contraction (in mm.)
1	7.5	4.5
2	6.0	4.5
3	5.0	12.0
4	4.5	17.0
5	4.0	21.0
6	3.5	29.5

However, the effect of a sequence of equal stimuli is not always as regular as in the example just given. Not infrequently one observes cases in which after some muscular contractions—the amplitude of which gradually increases—there follows unexpectedly a stimulus which is either entirely ineffective or at least much less effective. In other cases the effective stimuli form small groups which are separated from each other by one or two ineffective or only very weakly effective stimuli, so that the amplitudes of muscular contraction rise and fall alternately. Throughout, however, the relation between reaction time and amplitude of muscular contraction remains reciprocal.

REACTION TIME

HEIGHT OF MUSCULAR CONTRACTION

5 10 15 20 25 30 35 40 45 50
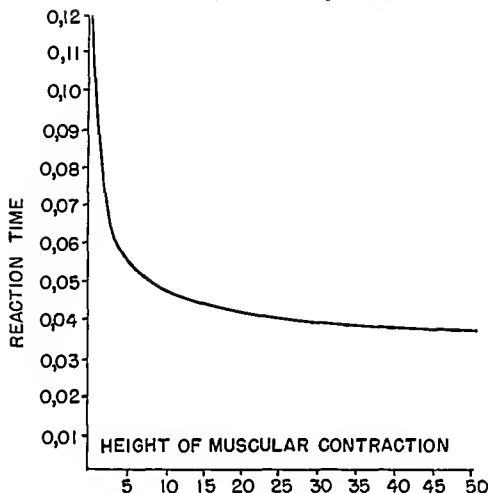
Fig 68

Relation of Change of Reaction Time to Change of Amplitude of Contraction. Plotting on the basis of our numerous observations the reaction time as ordinate and the height of muscular contraction as abscissa, the curve obtained descends as the amplitude of contraction rises from the minimum (fig. 68). In the beginning (at 0.12 sec.) the curve descends very steeply, to become then convex toward the abscissa so as finally to approximate 0.04 sec. asymptotically. This refers to state 1 of morphine-narcosis.

Reaction Time After Removal of the Cortex. The problem arises whether the elements of the cortex are involved in electrical stimulation of the surface of the brain or whether the effects of these stimulations are merely due to aberrant currents which impinge on the subcortical white matter. Clues to an answer can be expected by comparing the reaction time after stimulation of the cortex and of the white matter. The first to do this successfully were Franck and Pitres in their frequently cited work. In their experiments the reaction time was distinctly shortened after the

cortex had been removed: in an example given, from 0.065 sec. after stimulation of the cortex to 0.045 sec. after stimulation of the white substance. However, this does not constitute a definite proof of excitability of the cortical elements. Franck and Pitres nowhere take into account that the reaction time changes with the intensity of excitation expressed by the height of the muscular curve. Of two published curves which they obtained by stimulating the cortex and the white matter respectively, the latter is distinctly higher than the former. At an abscissa of 10 mm., the curve corresponding to stimulation of the gray matter attains a height of 6 mm., while the curve corresponding to stimulation of the white matter attains a height of 9 mm. The latter curve therefore ascends much more steeply than the former—a fact from which one is justified in concluding that the maxima of contraction (not given in the drawings of the authors) in both cases would show the same differences

Since in stimulating the gray matter alone, a shorter reaction time corresponds to a higher contraction, the shorter reaction time after extirpation of the cortex may be due only to the fact that the same electric stimulus evoked a higher contraction.

An unequivocal proof of the influence of the cortex upon reaction time could only be given by obtaining entirely congruent muscular curves from the gray and white matter and by comparing the reaction time corresponding to these curves. In spite of many attempts, we have never been able to bring that to pass As a general rule the amplitudes were distinctly higher after extirpation of the cortex and, concurrently, the reaction times were distinctly shorter In the series of curves, however, which we obtained before and after extirpation of the cortex, it is nevertheless not infrequently possible to find pairs of curves of the same amplitude of contraction. As fig 69 indicates, however, these curves show almost always a different course in respect to time in spite of the fact that the maximal ordinates are the same. The curve (a) obtained from the cortex is more drawn out. particularly in its descending part, than the corresponding curve (b) obtained from the white matter. Concomitant to this change in the form of the curve, there is a distinct shortening of the reaction time. It decreases from 0.08 sec. to 0 035 sec. For the time being we will only conclude from these changes that in stimulating the surface of the brain it is the cortex itself which is stimulated and not the white matter that is agitated by stray currents, for if the latter were the case the effect of cortical extirpation would be entirely unintelligible.

Discussion of the Above Results Before proceeding further. it may be useful to consider which part of the motor apparatus is responsible for the decrease in reaction time with increasing intensity of stimulation—a question which, however, cannot be answered as well as one might wish. So

far as we know at present, this may concern the muscle, or the conducting nerve-fibers. or, still more likely, the central apparatus.

The muscle is probably but little concerned. As has been shown previously by many authors. the latent time of a muscle increases with decreasing amplitude. However. its highest value is far too small to explain the occasional large increases in reaction time observed in our experiments. Unfatigued gastrocnemii of frogs yielded latent values of 0.004 to 0.014 sec., depending on the height of contraction. If one and the same gastrocnemius was systematically fatigued. its latent time increased from 0.008 to 0.021, while its amplitude decreased from 10 to 3 mm. These figures could be compared with our values of the reaction time for low and high amplitudes if in our experiments fatigue played any role at all, and
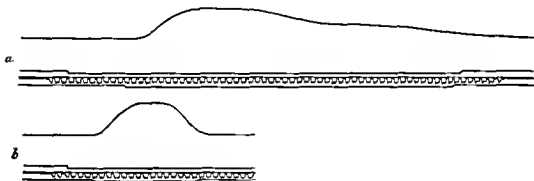
Fig. 69—Stimulation of gray matter, *a*, and white matter, *b*

if mammalian muscles have similar reactions Especially designed experiments convinced us that 80 to 100 contractions of the extensor muscle of the toes, elicited between two determinations of the reaction time, did not measurably increase it. Our experimental (cerebral) series, however, in no case comprised even one-fourth that number of contractions. If we add to this the observations of Bernstein and Steiner that the sternocleidomastoid muscle, exposed. cut out. cooled, and submitted to unfavorable conditions of nourishment. showed a latent period of 0.017 to 0.028 sec . it becomes clear that our high values of reaction time after weak stimulation. rising as they do to 0.1 sec. and more, cannot possibly be due to an increase of the latent time of the muscle alone. It was not within our program to determine by direct stimulation of the muscle the exact amount which the latter contributes to the reaction time, but it does not seem to be more than a matter of thousandths of a second. Be that as it may. the high values which the reaction time may attain in cases of weak stimulation must be due to other causes. Could it be a slowing down of conduction rate in the nerve fibers? Whether the conduction rate within these

fibers changes with intensity of stimulus is a debated question. However, the mere fact that a number of observers using the most refined experimental technique could not detect an influence of the intensity of stimulation, shows that this influence at most cannot be large,—much too small, in any case, to explain the enormous prolongation of the reaction time after weak stimulation.

Nothing else remains, therefore, but the assumption that this prolongation which is occasionally observed depends largely on the central apparatuses in which the excitation of the cortex takes its origin and which they transmit through the conduction pathway from fiber to fiber (cf. "accelerated excitation," below, and "decelerated excitation," p. 189).

State of Heightened Reflex Excitability (i.e., of Accelerated Excitation)—It is now necessary to investigate the reaction time under conditions other than those considered thus far, especially under other degrees of morphine narcosis.

As mentioned previously, the injection of morphine induces sometimes a state of considerably heightened reflex excitability (state 2) in which the animals react to any sensory stimulus, intended or unintended, by widespread muscular contractions. Acoustic stimuli are particularly effective. They make the animals wake up at once from their sleep, into which, however, they sink back after a short while.

In this state of narcosis the reaction time for minimal contractions is difficult to determine, if only for the reason that very small contractions are scarcely obtainable. For high amplitudes the reaction time decreases to 0 02 to 0 025 sec—that is to say, distinctly below the average value obtained under a good deep narcosis. We must mention, however, that even in good narcosis one can obtain occasionally such low figures if the intensity of the electric current is stepped up sufficiently. But these intensities are certainly higher than would be legitimate if stimulation had to be limited to the cortex. In the state of heightened reflex excitability electric currents of low intensity are sufficient to lead to such short reaction times.

These minimal values for the reaction time are of no small interest. In medium-sized dogs—which we generally used—the distance between the focal region for the front leg in the cortex and the m extensor digitorum communis longus is about 400 mm. Within the motor nerve fibers excitation travels at the rate of about 30 meters per second. If the whole nervous pathway from the surface of the brain to the muscle consisted of nothing but myelinated fibers, excitation initiated at that surface would arrive at the muscle after a duration of 0 0133 sec. Supposing, further, that the latent time of the muscle is 0.01 sec., we would obtain—still adhering to our first set of assumptions—a reaction time of 0 0233 sec..

a figure exactly equal to that which we found for our minimal value. In a state of medium narcosis it was shown by extirpating the cortex that it must contain elements in which the excitation rises more slowly than in the subcortical white fibers. The figures just given show that the delay which the excitation normally undergoes in the cortical elements may under certain conditions be reduced to a minimum or completely abolished. A definite demonstration of delaying or inhibitory processes will be given later in a much more conclusive manner. Suffice it to remark here that such an inhibitory action is not due solely to cortical elements, for, if that were so, extirpation of the cortex would invariably decrease the reaction time to its

Fig. 70

minimum of 0.02 sec., but that is by no means always the case. We would therefore hardly be wrong in the assumption that the ganglion cells intercalated in the pathway of the conducting nerve fibers constitute another mechanism for the delay of the muscular reaction, and that the effect of these cells also vanishes in state 2.

State of Decelerated Excitation—The opposite of the narcotic state 2 (i.e., state 3) is one which we cannot induce with certainty by changing the dose of morphine. We can only say that that stage occurs generally after large doses, and only after some time. It is characterized by an extraordinary delay of the process of excitation (see fig 70a). The reaction time becomes very long (in the example given, 0 17 seconds), the curve ascends very gradually, just as in a slowly waxing tetanus, and shows a very long duration.

When the cortex is extirpated (fig. 70b), both the reaction time and the total sweep of the curve become appreciably shorter. This phenomenon affords drastic demonstration that in the stimulation the cortical elements are involved and that they do influence the reaction time. We wish to emphasize, however, that after extirpation of the cortex the curves are not always as much shortened as in the example of fig. 70—a fact which goes

to show that under the influence of certain doses of morphine the reaction may be delayed within the subcortical ganglia also.

In state 3 the usual connection between reaction time and amplitude of contraction cannot be demonstrated. Quite frequently cases occur in which both values change in the same direction, so that a higher amplitude is associated with a longer reaction time. Everything goes to show that in state 3 the cortical elements are excited under very complicated conditions. Other similar cases will be discussed later.

Influence of Sensory Stimulation on the Process of Excitation— After having repeatedly determined the reaction time in a dog, we exposed and cut the sciatic nerve. Immediately after this operation the reaction time was appreciably prolonged, the amplitude of contraction decreased, and the curve of contraction expanded. Since then we have observed in many, but not in all, experiments the same phenomenon as a consequence of mechanical stimulation (pulling) of the sciatic nerve.

Example Small dog, 11 cgm morphine hydrochloride   column of 10 Grove's (16 to 19 volts), variable resistor, 1160

Series	Stimulation of Cortex	Reaction Time (in 0 01 sec)	Amplitude of Contraction (in mm)
I	1	3 5	33
	2	3 5	31
	3	3 0	35
	(Pulling of Sciatic Nerve)		
	4	12 0	1 0
	5	9 25	5 0
	6	8 0	16 0
	7	7 5	18 0
	8	7 0	23 0
	9	6 5	{ off
	10	5 5	{ scale
II	1	4 5	35 5
	2	4 0	38 0
	(Pulling of Sciatic Nerve)		
	3	10 0	7 5
	4	9 5	9 0
	5	9 0	14 0
	6	8 5	17 5
III *(after a pause)*	1	4 0	31 5
	2	4 0	37 0
	(Pulling of Sciatic Nerve)		
	1	12 0	2 5
	2	8 0	11 0
	3	8 0	15 5
	4	7 75	21 0
	5	6 5	19 0(?)

Obviously, pulling of the sciatic nerve changed the internal conditions of the motor centers. Excitation rises more slowly and to a lesser intensity than before the sensory stimulus. This change disappears after a time, since

the muscular contractions occur more quickly and with greater amplitude upon subsequent stimulations.

A very similar phenomenon is observed if, during a series of cortical stimulations, the abdomen is vigorously compressed.

Example: Middle-sized dog, 12 cgm morphine, 10 Groves (16 to 19 volts), variable resistance, 1000

Stimulation	Reaction Time (in 0 01 sec)	Amplitude of Contraction (in mm)
1	6 5	1 0
2	4 5	15 0
3	3 5	20 5
4	3 25	31 0
(Vigorous Compression 5	7 5	0 75
of Abdomen) 6	7 5	1 0
7	6 0	4 0

The effect seems to depend partly on the degree of narcosis, but still more on the intensity of the sensory stimulus. If the animal is in state 2 it is impossible to influence the process of excitation of the motor centers through a sensory stimulation. Also if the sensory stimulus is very strong there will be no effect, or even the opposite effect—namely, an increase of amplitude and a decrease of the reaction time. This effect was observed when during a series of cortical stimulations the sciatic nerve was stimulated by rather strong electric currents and the muscle frequently contracted reflexly.

Example: A dog of middle size, 12 cgm morphine, 10 Groves (16 to 19 volts), variable resistance 4160

Stimulation	Reaction Time (in 0 01 sec)	Amplitude of Contraction (in mm)
1	6 0	1 0
2	6 75	1 0
3	8 5	minimal
4	6 5	1 5
(Electric Stimulation 5	4 75	17 5
of Sciatic Nerve) 6	5 5	13 0
7	5 25	8 5
8	4 75	17 5
9	4 5	15 0

Deductions from the Facts So Far Reported and Further Facts Concerning the Excitability of the Cortical Substance—A number of the facts so far reported furnish, to our mind, a definite proof that electric stimulation of the cerebral cortex at the loci described by Fritsch and Hitzig excites the cortical elements proper and not the elements contained in the underlying white matter. For if the latter alternative were true, it should not make any difference, so far as the temporal sequence of excitation and the shape of the muscular curve is concerned, whether the electrodes are put onto the surface of the brain proper or, after extirpation of the cortex, on the exposed white matter. We have shown, however (partly confirming Franck and Pitres) that the reaction time as well as the duration of the

muscular twitch is shortened when the cortex has been removed. Only in state 2 it does not matter whether the cortex is present or absent, and the reaction time is the same in both cases and is minimal. In state 3, however, the excitation in the cortex rises more slowly and disappears more slowly than in the fibers of the white matter. It is thus beyond doubt that the gray matter influences the process of excitation, and this must obviously be due to some activity of these very elements. The cortex must play a role other than only that of a moist conductor of stray currents reaching the white matter. We cannot yet define more clearly the nature of those processes which go on within the cortical elements. We have a few times encountered animals in deepest narcosis in which it was impossible to elicit muscular contractions from any points on the surface of the brain, even when using much stronger currents. Yet when the cortex was removed, very weak currents through the white matter sufficed to elicit a contraction.

Examples· Experiment of February 17, 1881. A small dog which received 12 cgm of morphine yielded no muscular contractions from the surface of either the left or the right hemisphere when a series of six Grove's (10 to 12 volts) were used with all the variable resistance in. Even when metal electrodes were used instead of nonpolarizable thread electrodes in order further to reduce resistance, the results remained the same. The left cortex was then removed. The white matter reacted easily after putting in only 500 mm. of platinum wire of the variable resistor, while the surface of the right hemisphere was still entirely refractory.

Experiment of March 18, 1881. In another dog 16 cgm of morphine were given subcutaneously and afterwards 18 cgm. intravenously. The surface of the left hemisphere did not respond to 12 Grove's (19 to 23 volts) at a resistance of 10,000. The white matter responded at a resistance of 370.

It would, of course, be of great interest to induce with certainty this functional obliteration of the cortex which we have unexpectedly found in cases of very deep morphine narcosis. However, determination of the precise doses of morphine required to induce certain states meets with insurmountable obstacles. Individual differences of the animals are a great obstacle, as they cause marked variation in the response to morphine. Furthermore, morphine does not have cumulative effects when given in successive doses. However, it is possible to get at least approximately the desired result by means of chloral.

In a dog which had been given 12 cgm. of morphine, a subsequent dose of 0 6 chloral hydrate caused the excitability of the cortex to decrease to such a degree that it failed to react to the current delivered from 12 small Grove's (19 to 23 volts) with all resistance in. However, when the nonpolarizable thread electrodes were replaced by metal electrodes, a very

slight motor reaction was elicited. After the cortex had been removed a resistance of 870 sufficed to elicit maximal contractions. In another dog injection of 0.14 morphine and 0.1 chloral lead to a state in which 12 Grove's with a resistance of 11,000 elicited no reactions, and with a resistance of 15,000 elicited only minimal reactions from the cortex. Stimulation of the white matter elicited maximum contractions with a resistance of as low as 500. A third animal was given 0.12 morphine and 1.05 chloral. The motor region of the left hemisphere was rendered entirely unexcitable for a current of 12 Grove's (19 to 23 volts) with all resistance in. The white matter yielded powerful contractions at a resistance of 2000. An increase of chloral finally made stimulation of the white matter ineffective.

The facts just given allow, to our minds, of only one interpretation. They demonstrate the excitability of the gray matter itself, for after certain amounts of morphine and chloral, currents of the order of intensity which were generally effective in our experiments, and even much stronger currents, lose their efficiency when applied to the surface of the brain, while at the same time the white matter remains highly excitable. Under normal conditions, therefore, it is impossible that stray currents impinging upon the white matter are responsible for the effectiveness of the currents applied to the cortex. Moreover, these stray currents should be effective at the degrees of narcosis just described, which they are not, in spite of the high excitability of the white matter.

This reminds one of the behavior of the brain during the first days after birth, at which time, according to Soltmann, the cortex does not react to an electric current, while the white matter is easily excitable.

Some Observations on Epileptic Fits Following Electric Stimulation of the Brain

Too frequently our experiments were interrupted by epileptic fits which, however unwanted, gave us an opportunity to observe this phenomenon, the subject of so many previous investigations. Since they furnish proofs for the cortical origin of motor stimulation, we believe we are justified in reporting on our observations. They are not exhaustive but merely meant to supplement the numerous observations of previous investigators.

As is well known, after stimulation of a given point of the motor cortex, the epileptic seizure spreads in an almost constant sequence to the different parts of the body. After stimulation of a point on the left hemisphere, which in the right hemisphere led to closing of the eyes, the muscular contractions appeared generally in the following sequence (which, by the way, has repeatedly been observed by other authors): right eye, left

eye, right anterior extremity, left anterior extremity, posterior extremities. In addition to this, inspiratory seizure and profuse salivation appear. At times all muscular groups of one side are affected before the seizure spreads to the other side.

Under certain circumstances the muscular twitches which occur within a certain group of muscles may be restricted to that group and disappear after a while; in the majority of cases, however, the seizure spreads over the whole body in the way just described, loses its clonic character, and goes over into a tonic form which once more leads to clonic contractions as the seizure disappears. We cannot answer in a few words the question in which part of the central nervous system this stimulation of unknown nature takes place. The first point of origin undoubtedly lies in the cortex, which is subjected to an artificial stimulus primarily. It is here that processes take shape which at first lead to clonic contractions in the corresponding groups of muscles and which soon cause similar processes in the motor centers of the other muscle groups in the sequence just described. Just as the stimulating process in the primarily excited center is started by an electrical current, but then develops spontaneously under the influence of the previous artificial stimulus and goes on by itself after the electrical current has ceased, so it appears to develop in the centers which are secondarily excited. At first there is a concomitant stimulation caused by the center primarily activated, but in the course of the epileptic seizure the excitation becomes independent of that of the primarily excited center. The motor centers of the cortex are the first in which this secondary activity develops, but later the subcortical motor apparatuses also develop such activity. For this sequence of events the following facts furnish evidence.

According to Munk, it is possible to stop an epileptic seizure caused by stimulation of a certain part of the gray matter if the stimulated part of the cortex is extirpated at the right time; if, however, the seizure has been established for some time, such an extirpation will no longer interrupt it. From this it follows that (1) the primary seat of the excitatory cause is in the stimulated cortex; (2) during the seizure other cortical and subcortical motor centers are brought into a state of excitation which is independent of that of the primarily stimulated locus.

To Munk's observation we are able to add the following one: If the seizure has only lasted for a short time it is often possible to save one extremity from the fit by extirpating its cortical center, while the rest of the body keeps on being shaken by the most violent convulsions. At that time the other cortical centers are obviously already the seat of self-sustained excitation, for after local destruction of the cortex the seizures are stopped only locally; but the subcortical motor centers are not yet in self-sustained

excitation, for, if they were, extirpation of the cortex would not have a locally calming influence.

In other cases it is possible to stop the convulsions altogether by swift extirpation of the whole motor cortex of one side. It does not matter whether the extirpation is made on the side primarily stimulated or on the opposite side. Obviously in such cases excitation is still restricted to the cortex. Every motor region exerts an excitatory influence not only on the corresponding muscle groups of the contralateral side of the body but also on the motor cortex of the other side. When this influence is removed, excitation becomes so small that it very soon vanishes.

In a third series of cases the general convulsions go on even if the motor region of one hemisphere is completely excised. In such cases the subcortical motor apparatus must already have become the seat of self-sustained excitation.

The first point of origin of the motor excitation lies, therefore, undoubtedly in the cortex. At first it is restricted to the locus of the artificial stimulus. From there stimulation spreads in the cortical centers symmetrically on both sides—at first as concomitant excitation, later as self-sustained excitation; finally excitation becomes self-sustained in the subcortical motor centers, too. Albertoni reported that, even after removal of the cortex, stimulation of the white substance can cause epilepsy—a fact which was wrongly denied by Franck and Pitres. This seems to speak against the conception that the point of origin is in the cortex. We too have several times observed an outbreak of epileptic fits after stimulation of the white substance, but we have always observed a sequence different from that generally seen. While stimulation of the cortex of the left hemisphere led to contractions first of the muscles of the right side of the body, stimulation of the white substance of the left hemisphere caused first a contraction on the left side of the body. Sometimes this contraction remained restricted to that side; sometimes—and that more frequently—the contractions passed on to the right side of the body. This sequence of events indicates that the excitation began in the motor centers of the right cortex, which became excited through the association fibers in the white matter, which in their turn were stimulated on the left side. That this is the right interpretation can be proved by the fact that stimulation of the white matter after bilateral extirpation of the cortex never led to an epileptic seizure.

From this last observation it also follows that the subcortical motor centers can be brought into the state of excitation necessary for sustaining epileptic seizures only by way of the cortex. The cortex of each hemisphere is able to induce a state of excitation in the subcortical centers of both sides

of the body. This state is first induced in those of the opposite side of the body, and later, probably via the contralateral subcortical centers, in those of the same side.

When viewing the peculiar manner in which epilepsy begins and gradually spreads out, one may gain a few hints for the understanding of this process. It always begins as a series of contractions of a certain muscle group, slight at the start but gradually increasing. It seems, therefore, that the central excitation which elicits the first contraction increases the excitability of the center to such an extent that a secondary stronger process of excitation ensues in that center, that this second excitation creates a third one which is still stronger, and so on; in short, that each stimulation becomes the cause of the increase of the following one. We have a complete analogue in the electric stimulation. Even if stimulation is effected by currents which at first are not strong enough to elicit a contraction, every subminimal electric stimulation, nonetheless, causes changes in the motor center which makes the following one more effective, until finally a contraction is elicited which is weak in the beginning but which increases with the number of stimuli. Once the contractions of that muscle group, the center of which was originally excited, have attained a certain maximal height, contractions spread out to other muscle groups in a sequence similar to that observed in epileptic seizures There is only one difference between the general contractions which can be evoked by repeated stimulation of a given cortical center and the pathological epileptic seizures which originate in the cortex. In the first case an artificial stimulus is applied; in the second case certain local changes, such as inflammation, pressure, etc., act continuously. But when this continual stimulus happens to reach such an intensity that it actually evokes excitation, the process of excitation becomes in turn the cause for increased excitability, initiating the sequence of events just described.

II. INCREASE OF EXCITABILITY AND INHIBITION OF EXCITATION IN THE MOTOR CENTERS

Increase of Excitability by Tactile Stimuli

In the previous chapter we discussed the influence of stronger sensory stimuli on the excitability of the motor centers. It was shown (pp. 190-191) that mechanical or electrical stimulation of sensory nerve trunks or compression of abdominal viscera exert a powerful influence on the state of excitability of the motor centers. With equal stimulation of the centers immediately after such manipulations the muscle curve becomes lower and more drawn out and the reaction time increases. Only when, after

exceedingly powerful sensory stimuli, vivid reflex muscle contractions occur does the excitability appear to be increased. For both phenomena there are enough parallels in previous physiological experiences. The inhibitory action of strong sensory stimuli on the motor centers has been the subject of many investigations, and it has frequently been observed that previous motor excitations facilitate the effect of consequent stimulation.

There are no parallels, however, for observations which we could make about the surprising influence of very weak tactile stimulation upon the excitability of the motor centers. The peculiar character of these phenomena will justify the fulsomeness with which they are reported. In what follows we shall define with Fechner the threshold as that value of the stimulus which, impinging upon the motor centers, elicits a minimal muscular contraction. We shall call subminimal excitation the intensity of a current slightly weaker than that near the threshold The fact which we observed can be expressed by saying that in a certain state of morphine narcosis *a subminimal excitation becomes powerfully effective if, shortly before its application to the motor centers, the skin of certain parts of the body is subjected to lightest tactile stimulation* The dose of morphine must be chosen so that the animals lie quietly in a deep sleep However, the excitability of the cortex must not be completely abolished (cf. p. 191) The state of increased reflex excitability (state 2, p. 188) cannot be used.

Under the appropriate degree of narcosis, one determines the value of subminimal excitation for the cortical center of the right foreleg. Certain precautions must be observed. It is necessary to begin with low intensities and to increase these gradually by means of the variable resistor One stimulates at intervals of 4 to 5 seconds until one obtains minimal contractions. Then the moving contact of the variable resistor is pushed back again to a position which is certainly ineffective. To avoid summation of excitation, the exploratory stimulations must not follow each other too fast (cf. pp. 183-184). For similar reasons one must not search for subminimal intensities by beginning with high intensities and decreasing the intensity until contractions disappear. for previous strong excitations of the centers increase their excitability, so that in decreasing the resistance intensities are still effective which without these previous excitations would be entirely ineffective Proceeding in this way, one would find a threshold value too low and, therefore, a subminimal intensity which would also be too low. When the subminimal stimulation has been determined, and found stationary in trials repeated at intervals of several seconds. it is only necessary to stroke with one's hand, and only once, the skin of the paw whose cortical center is stimulated, to find immediately thereafter that the same current is greatly effective. This increase of excitability lasts for a few

seconds and then disappears. Occasionally the effect of a single light stroke
is only slight, so that the current previously ineffective becomes effective
but leads only to a low contraction. In such cases repetition of the tactile
stimulation leads generally to further increase of contraction. The curve of
fig. 71 represents what has just been said. The lower line drawn by an
electromagnet marks at 1, 2, 3, . . . 8 the single stimulations. Their effects
are shown on the upper line. The first stimulation was ineffective. Immedi-
ately before the second one the skin of the paw was stroked (marked by
str.), the stimulation became effective but the increase of excitability was
small, and the third stimulation was again ineffective. Immediately pre-
ceding the fourth stimulation the skin of the paw was touched lightly once
more. This time the increase of excitability was more pronounced, for the
contraction was high and lasted longer, the response to the fifth stim-
ulus was appreciable and the sixth stimulus was still slightly effective. Re-
newed stroking immediately before the seventh stimulation caused the
contraction again to increase appreciably, etc. The intervals between the
single stimulations were at least four seconds (between 1 and 2) and were
generally longer.

It is, incidentally, unnecessary to have such complicated apparatus in
order to demonstrate the fact which interests us here. The effect is a per-
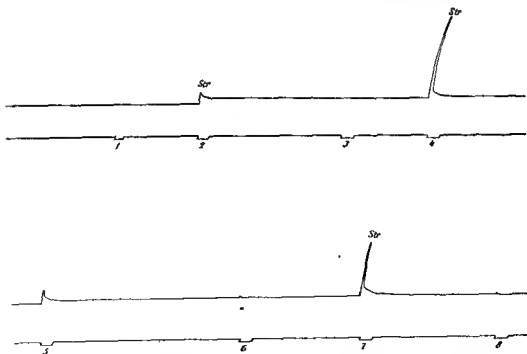
Fig. 71—This tracing has been cut in two. In the original this was one continuous tracing

fectly obvious one, so that one can perform the experiment very successfully on the whole paw without isolating a single muscle. "It is just as though the dog had to be told to raise its paw," a student very properly remarked when he saw that a current previously ineffective led to a powerful contraction immediately after a slight touch on the paw.

The excitability of the motor centers of the forepaw is affected not only by tactile stimuli to its own skin but also by tactile stimuli applied to the skin of the abdomen or chest of the same side, although these latter stimuli do not act with the same uniformity. Stimuli applied to the other side of the body have never been observed to be effective.

To the question which immediately poses itself—i.e., whether the increase of excitability should be ascribed to the cortical or to the subcortical motor centers—a definite answer can be given only in part, for entirely similar experiments made after ablation of the cortex still yielded a positive result. It is, however, more difficult to obtain this result, since it is harder and more time-consuming to get an exact anatomical localization on the cut surface of the white matter. Moreover, hemorrhages issuing from the cut surface often render stimulatory experiments difficult.

It follows that these tactile stimuli affect the subcortical motor centers. It is uncertain, although probable, that they also influence the excitability of the cortex if that organ is present.

Inhibition of Excitation by Sensory Stimuli

A number of other facts which can also be demonstrated under a similar degree of morphine narcosis are apparently in direct contrast to the phenomena just described. To our mind the most important phenomenon is this: all muscular actions of the animal become of a tonic nature. If after pressure on the paw the animal lifts that paw, the extremity remains for some time lifted and sinks down very slowly and hesitatingly. When the tendon of the common long extensor of the toes has been coupled with the recording apparatus, and when in any way whatsoever a reflex contraction of the muscle has been evoked, the writing device continues to record a tonic contraction of the muscle or else records a curve the ordinate of which decreases very gradually. The same phenomenon of tonic contraction appears if the muscle becomes excited concomitantly with deep inspirations. Similarly, contractions evoked by stimulation of the cortical center remain for a long time, particularly if the stimulation is repeated several times at short intervals. The first twitch leaves a small, the second one a somewhat larger contraction, until after four or five stimulations the muscle remains permanently and powerfully contracted. Thus all stimuli which under normal central conditions evoke only fleeting excitations, lead

now to the development of a persisting state of excitation. We have frequently observed that a strong sensory stimulus—for instance, a pull on the sciatic nerve—led to that desired central condition even when the morphine narcosis had been insufficient to bring it about.

When in some way or other the muscle had been subjected to a state of permanent contraction, and when one then stroked lightly over the skin of the back of the paw, relaxation suddenly occurred. Either the muscle became fully elongated at once or, after a single tactile stimulus, suddenly elongated to a smaller or larger fraction of the total amount of its previous contraction. Repetition of the stimulus led to a further relaxation, until the
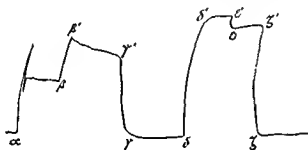
Fig 72

muscle was completely relaxed. In view of the great interest which these phenomena command, it may be permissible to report some of our experiments.

Figure 72 was recorded on a very slow drum. At α electrical stimulation of the cortical center evoked a muscular twitch and a considerable lasting contraction. This contraction was increased by another stimulation (at β) by the amount $\beta\beta'$. The muscle relaxed spontaneously very slowly ($\beta'-\gamma'$). At γ' the paw was stroked. This produced a sudden relaxation, so that the muscle became even slightly longer than it had been before the first stimulation. This latter phenomenon recurs in later examples. It was due to the fact that, under the degree of morphine-narcosis used here, slight contractures were very frequently present before the first stimulation. At δ the paw was squeezed forcefully: reflex contraction ($\delta\delta'$). The muscle remained shortened. At ϵ and ζ stroking of the skin of the paw: the muscle elongated at first by the small amount $\epsilon'\epsilon$, the second time by the larger amount $\zeta'\zeta$.

Figure 73. At α a reflex contraction was evoked by strong rubbing of the abdominal skin ($\alpha\beta$). During the slow relaxation, tactile stimulation of the skin of the paw at γ' resulted in rapid partial elongation ($\gamma'\gamma$), and then slow further elongation ($\gamma\delta$). At δ reflex increase of the contracture ($\delta\delta'$) by strong squeezing of the paw. At ϵ slight stroking of the skin of the paw

produced immediate complete relaxation (ϵ'). At ζ once more reflex contraction, at η' completely released by stroking of the skin of the paw.

Figure 74. At α evoking of a reflex contracture (αα'). At β', after tactile stimulation of the skin of the paw, the muscle suddenly increased its length by the amount β'β, but then became again slightly shorter—not a rare phenomenon. Repeated stroking of the skin of the paw (γ'-δ'-ϵ') evoked each time a partial elongation until finally the muscle was completely relaxed.
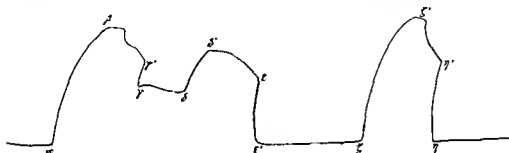
Fig 73
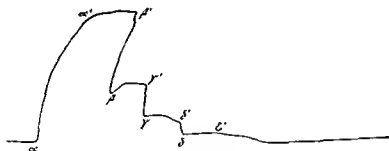
Fig 74

Fig 75

Figure 75. At α and γ reflex contractions were evoked. At β' and δ' they were suddenly released when the face of the dog was forcefully blown at.

Slight tapping on the nose, acoustic stimuli, or *very weak* electrical stimulation of the sciatic nerve are just as effective as slight tactile stimulation of the skin or blowing on the face. With electrical stimulation of the

sciatic nerve one has to be extremely careful in order not to go above that intensity of current which is just effective. Between the secondary coil of the inductorium and the electrode applied to the central end of the right sciatic nerve, we put a key in series and then very slowly decreased the coil distance while the muscle was in contraction, opening the key momentarily after each step of approach. In this way one arrives at a position at which the contracted muscle relaxes. Pushing in the coil somewhat further, one can easily find another intensity of current which does not lead to a relaxation but to an increase of contraction.

Obviously various weak peripheral stimuli are capable of stopping tonic excitations of the motor centers, but which centers are thus affected, the cortical centers or the motor mechanisms at lower levels? We can say this: in a number of cases in which every contraction of the muscle becomes tonic, this phenomenon ceases after extirpation of the cortex. In other cases it remains undiminished. Then the weakest peripheral stimuli have an inhibitory effect. Thus, the motor apparatus of the cortex, as well as that at lower levels, appears to be subject to that peculiar state in which transitory actions cause persistent excitations.

Finally, it has to be mentioned that we have met with some, although only a few, cases in which persisting contractions could easily be evoked but in which relaxation could not be brought about. We are unable to define more precisely the conditions of such negative experiments.

Inhibition of Excitation by Central Stimulation

It is well known that we are able not only voluntarily to innervate our muscles but also voluntarily to put muscles out of action. The question, however, whether the voluntary interruption of muscular activity is due simply to the cessation of impulses from the motor centers or to positive antagonistic effects which inhibit the action of these motor centers, has hardly ever been seriously considered and much less subjected to experiments. The observations reported in the last paragraph show that it is indeed possible to evoke from the periphery antagonistic effects, putting motor centers out of action. These peripheral stimuli were surprisingly small; in fact, much smaller than those which elicited activity of the centers from the same receptor apparatus. The foregoing observations necessarily lead to the question whether slight direct stimulation of the motor centers might not act in a way similar to slight peripheral stimuli and terminate an excitatory state.

Experimentation gave a positive answer. If either reflexly, or by a strong electrical stimulation of the cortex, a continuous muscular contraction was induced, it could be released by a much smaller stimulation of the

self-same cortical point. This occurred either completely after a single stimulus or in steps after repeated stimuli.

Figure 76. Ten Grove's (16-19 volts) in series. Position of variable resistor at 1000. Stimulation of the left center for the foreleg at *a*, shortening of the muscle by the amount *aa'*. When relaxation began, renewed stimulation at *b*, and contraction by *bb'*, very gradual descent of the curve from *b'* to *c'*; at *c'* stimulation of the same cortical point (on which the electrode had immovably rested) at a position of the variable resistor at 350: immediate elongation by *c'c*.
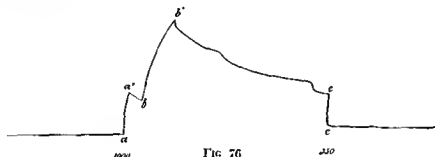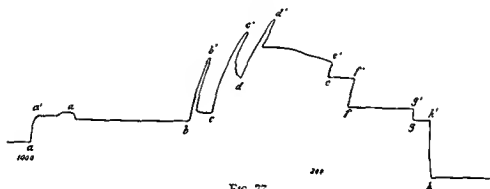
FIG 76

FIG 77

Figure 77. The curve was taken from the same dog as in fig. 76. It began while the muscle was still a little contracted by a previous stimulation. At a stimulation with the variable resistor at 1000: contraction *aa'*, which apart from a small transitory oscillation (at *a*) remained constant until *b*. At *b*, *c*, and *d* repeated stimulations; after each stimulus the contraction became stronger and then descended very slowly to *e'*. At *e'*, *f'*, *g'*, and *h'*, stimulations with the variable resistor at 300. After each stimulation sudden elongation until finally the muscle was more completely relaxed than at the beginning of the curve.

Since in all experiments constant currents of short duration were employed, one might be tempted to seek an explanation for the inhibitory

effect of these currents in electrotonic effects by which some nerve-fibers connected with the cortical centers might be affected. However, the same inhibitory effect can with sufficient caution be obtained by alternating current. This may be done in two ways. At a suitable distance between movable and primary coils a contraction may be elicited by allowing the induction currents to go through the cortex for about two seconds. It is often possible to release the contraction at the same position of the movable coil if the key between the secondary coil and the electrodes is opened just momentarily so that only a few pulses impinge on the cortex. In other cases
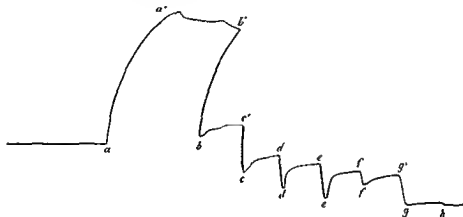
Fig 78

it becomes necessary to diminish the intensity of the induced current in order to obtain the desired effect. The following example was chosen because it is interesting for more than one reason. For with all methods to release contractions it happens now and then that the muscle relaxes at the moment when the inhibitory stimulus is applied but contracts again immediately afterwards. One obtains then curves of the peculiar configuration shown in fig. 78.

At the beginning of the curve the muscle was still fairly strongly contracted Upon stimulating the center by an induction current (at *a*) the contraction became vastly increased (*oa'*). At *b'*, *c'*, *d'*, *e'*, *f'*, *g'*, a few induction pulses are sent through the cortex by momentarily opening the key. Each time there occurred a sudden relaxation and then a renewed contraction, but each time the contraction became smaller than the previous elongation, so that finally the muscle relaxed completely. Without going beyond statements of fact, it can only be said that stimulation of the same cortical point either elicits excitation of the motor center or removes an existing excitation, depending on the intensity of the current employed.

But it remains entirely problematical whether the same or different anatomical elements of the cortex are involved in both processes. It could be argued that in the same region of the cortex there exist on the one hand excitatory cells and on the other hand inhibitory cells, and that with stronger stimuli the effect of the former, but with weaker stimuli the effect of the latter, predominates. Or one might assume that within the same ganglion cells stimulation of different intensity evokes processes of different kinds. But things become still more complicated: inhibition of contractions can be induced not only by electric stimulation of the same cortical points which at stronger stimulation evoke these contractions, but also by stimulation of any other parts of the cortex if only by careful trial the proper intensity is found—a matter of great patience on the part of the experimenter. We have tested in that respect the most diverse points of the anterior as well as the posterior brain. It is true that on the basis of these experiments one could still argue that in stimulating a region of the cortex far from the motor centers, stray currents may go from the point of stimulation to that center and may thus induce the inhibitory effect in the same manner in which very weak currents directly applied to that center act. It is hardly possible to refute this argument completely, yet it can be made very improbable by the following observation. A dog was given 13 cgm morphine. Contractions of the extensor digitorum communis longus could be relaxed from the center for the foreleg by using 8 small Grove's (13–15 volts) with the variable resistor at 165. The same result could be obtained from the anterior part of Munk's visual sphere [probably area 19—trans.] with the resistor at 2000. At this latter point a piece of the cortex (of the size of a one mark piece [slightly larger than a quarter of a dollar]) was cut out by a flat cut with a scalpel, and was then replaced as evenly as possible on the cut surface. When electrodes were applied once more at this point, the contractions could no longer be relaxed, not even with maximum resistance, and that in spite of the fact that appreciable stray currents reached the motor region as shown by a frog's leg used as an indicator. Thus after disrupting the anatomical continuity but not the physical conductivity, enormously increased currents were ineffective, while with intact anatomical continuity much weaker currents brought about that effect. It follows with at least great probability that the release of contractions from the various parts of the cortex is due to a stimulation of these very regions which exert an influence on the motor apparatus by way of association fibers. This probability is heightened by the circumstance that contractions are relaxed by the most diverse sensory stimuli, for these sensory stimuli undoubtedly affect first of all the cortical areas belonging to them. It is only from these that the motor apparatus can be affected.

III. SOME CONCLUSIONS FROM THE EXPERIMENTS HERE REPORTED

Concerning Central Processes in Motor Excitation

We are well aware that the observations reported in the first two chapters are still far from giving us even a partial insight into the properties of the motor centers of the brain. On the contrary, we have emphasized that our conceptions of the nature of a motor center are thus far entirely fragmentary, nay, almost meaningless.[1] Our first experiments were concerned with the question of the localization of the cerebral motor centers, whether such centers existed in the cortex (which some authors deny) or whether they were present only in some subcortical part. We concluded that the gray matter was very definitely a mediator of motor impulses. In the first place, the temporal sequence of the excitation (reaction time and shape of the curve) is generally different when it is the cortex than when it is the white matter that is stimulated. Secondly, at times the cortex becomes refractive even for very strong currents, while the subjacent white matter reacts vigorously to much weaker currents. Thirdly, epileptic seizures were shown to have their point of origin in the cortex although, as they progress, subcortical centers can become springs of excitation.

We do not wish to enter into a discussion of the nature of the impulses issuing from the cortex—a discussion which at present could not be brought to a conclusive end. Nonetheless, we would like to mention a conception advanced by several authors merely in order to emphasize its questionable value. Following Meynert and Wernicke, H. Munk maintains that movements are induced from the cortex only by "motor images" which originate in the cortex and that "with the origin of a motor image of a certain intensity that particular movement is immediately executed if it is not inhibited from somewhere." Drawing the full consequence of this conception, Wernicke, in his excellent textbook on the diseases of the brain, has pronounced the opinion that the electric stimulation of the cortex in its motor regions at first "evokes memory images of movements, motor images which evoke complex muscular effects by centrifugal fibers issuing from the ganglion cells which are involved." Quite apart from any other consequences, this conception seems to run foul of the results of our experiments. For we have reported that electric stimulation of the same cortical point either induces movement or inhibits a movement induced in some other way—depending entirely on its intensity. Should the electric current evoke in the first case

[1] Quite recently Christiani made the attempt to define mathematically the nature of the psychomechanic central apparatus. We shall have to wait for his more extensive publication before the ideas of this author can be compared with the viewpoints to be developed subsequently.

the image of a movement and in the second case the image of quiescence? It would be hard to find anybody who would dare to answer this question affirmatively.

In any event, investigations of the physiological processes in the brain should ignore as much as possible the contents of consciousness correlated with these processes if their goal is to interpret physical events. Whether it is an image or whether it is the will which induces a movement, in either case the psychic process will go hand in hand with a physical process in the cortex. It is this physical process which is the immediate cause of the motor excitation, and which is obviously the immediate object of physiological investigations. The less physiology employs psychological conceptions, the surer will be the basis which it will one day be able to lay for a physiological psychology in the wider sense of the word.

When, in that spirit, we try to analyze the processes in the motor centers, it has to be emphasized that the motor nerve fibers which supply the various muscles and muscle-groups of the body do not find their first connections for the purpose of coordinating movements in the cortex but at lower levels. However, as we observed, cortex and subcortical centers have certain general properties in common.

Thus under normal conditions a transient stimulus which, directly or indirectly, acts on the motor centers, evokes only a transient state of excitation. Under certain conditions, however, every excitation of the motor centers assumes permanence.

If one clings to the conceptions of excitability deduced from experiments on nerve fibers, one will be prone to think that the tonic character of central excitations is due merely to the increased excitability of the center. However, the expression "increased excitability" does not explain very much. Moreover, "increased excitability" presupposes that weak stimuli are unusually strongly exciting. But we have seen just the opposite, namely that very weak peripheral or central stimuli may terminate a pre-existing excitation. This phenomenon does not fit into the conception that we simply have to do with "increased excitability." Rather, it proves that a weak stimulus must induce processes different in their nature from those which correspond to excitation.

Both phenomena—the tonic character assumed under certain circumstances by all excitations, as well as their disappearance after weak stimuli —indicate an unexpected complexity of the process of central innervation.

It appears that under normal conditions every central excitation finds or creates within the excited centers conditions which, as soon as the stimulus has disappeared, make this excitation vanish or decrease below

threshold. If such a precise delimitation of central motor or sensory excitation did not exist, we would neither be able to execute intentionally movements of measurable duration nor would our sensations correspond to the temporal sequence of the extraneous stimuli producing them.

This very obvious train of thought leads to the conception that in central processes excitation must be coupled with another event which exerts a dampening influence on the induced excitation. The exact nature of these inhibitory influences, however, we are unable to define in detail, and we hope all the more to be excused since the exact nature of the excitatory process is also undefined. In any event, that process which is called excitability or excitation of the motor centers must be some sort of a molecular movement within the ganglion cells. In the dead cell this movement has come to a standstill. In the living cell it goes on with an energy varying according to circumstance. If that energy surpasses a given value then excitation in the nerve fibers issuing from the cell is induced. The closer the amount of kinetic energy of these internal movements is to the limiting value, the less intense will have to be those stimuli which can accelerate them sufficiently to cause them to attain that limiting value; the higher, in other words, will be the excitability. Inhibition of excitation would be nothing but the diminution of the kinetic energy of the molecular movements below the limiting value. Inhibition may in essence be nothing but resistance against molecular movements, or, more likely, an acceleration of the molecules in a direction opposed to the direction of their movements, leading, of course, to a diminution of their kinetic energy.

But whatever the true explanation, if the normal ratio of excitatory to inhibitory processes changes in favor of the former, then these will attain an unusual duration. This seems to be the sort of thing that occurs in state 2 of morphine narcosis [hyperexcitability]. In that case, the absolute intensity of the excitatory process may decrease. If, however, the energy of the inhibitory processes decreases still more, the effect as far as the stimulation of the motor nerve fibers is concerned will remain as in state 2.

Excitations affecting indirectly (tactile, acoustic, etc.) or directly (electric) the motor centers will cause tonic excitations to disappear; therefore, these stimuli increase suddenly the relative energy of the inhibitory process. Correlating this fact with the other—that during morphine narcosis those weak sensory stimuli which incessantly impinge upon the peripheral sense-organs (movements of the air, radiating heat on the skin light and acoustic radiations on the eye and ear, etc.) lose their effect—one is led to assume that under normal conditions the inhibitory processes in the motor centers are kept at a certain relative height by these continuous sensory excitations. If these excitations are taken away during morphine-

sleep the relative energy of inhibition decreases and can be increased to normal level only by purposely induced stimuli of a certain intensity.

If this seems to be pushing an hypothesis too far, we may refer to the facts alluded to in the following paragraph.

The assumption of inhibitory processes accompanying excitatory processes in the motor centers of the brain appears also to make intelligible the differences in the effect which a stimulation of the cortex and a stimulation of the subjacent white matter induce. Excepting the state of increased reflex excitability which is occasionally induced by morphine, stimulation of the cortex led to an excitation which differed in its duration and in its intensity from that induced by stimulation of the white matter (cf. pp. 186 and 189) Other conditions being equal, the reaction time is longer, the contraction of the musculature generally smaller, and the muscular curve drawn out longer in the latter than in the former case. These differences can be understood by the assumption that direct cortical stimulation induces not only processes of excitation but simultaneously processes of inhibition. These processes distribute the development of the kinetic energies in the excited elements over a longer duration by increasing them at a later moment above threshold (prolongation of reaction time), and on the other hand keep them above that value for a longer time (drawing out of contraction curve), while simultaneously the absolute intensity of the excitation becomes smaller (decrease of muscular contraction). In these experiments, too, sensory stimuli of a certain intensity are effective They lead to an increase of inhibition; hence (p. 190) the muscular contractions decrease and the reaction times and durations of the contractions increase simultaneously. The assumption of inhibitions as part and parcel of the mechanisms of central innervation affecting by their relative value— i e , by the ratio of their intensity to that of the excitations—the quantitative aspects of the process of excitation both in its intensity and its temporal sequence, enables us to understand many other things which heretofore were enigmatic. If we assume, as we are almost driven to do, that inhibitions delimit not only the temporal but also the spatial spread of excitation, then it becomes clear that in deep morphine narcosis excitations spread unusually easily from the primarily excited centers to other ones Quite correctly Munk pointed out that the tendency to respond to local stimulation of the cortex with general epileptic seizures is particularly noticeable in dogs subjected to large doses of morphine A state of increased excitability which can be observed in many individuals as a consequence of morphine also indicates an easy spread of the state of excitation from the sensory to the motor centers. Some of the facts which we reported may appear to contradict the theory just sketched. For our assumption

appears to be incompatible with the observation that subliminal excitations impinging upon the motor centers are immediately effective if shortly before stimulation the skin of the region whose muscles are involved is exposed to a tactile stimulus.

However, between well ascertained facts there can never really be a contradiction. A contradiction can only exist between assumptions deduced from these facts. In the present case it has to be remembered that the effect exerted on an object by a certain process depends not only upon the nature of that process but also on the state in which the object happens to be at the moment when the process impinges upon it. When that state has in any way been altered, then the result of the effect, too, will necessarily be different. The excitation conducted to the motor centers through sensory fibers may very well have a different effect if the centers are in a state of quiescence or in a state of activity. In the first case the kinetic energy of the internal molecular movements is relatively small and below threshold. The impulses conducted to the center by sensory fibers, if sufficiently strong, will increase the amount of kinetic energy above threshold; in other words, reflex movements will ensue. If the impulses have a lesser intensity, then they will increase the kinetic energy to a lesser degree, so that it remains below threshold. The excitability of the center is increased (see fig. 71). It is different when the centers are in tonic activity. Strong impulses reaching the ganglion cells from the periphery are still able to increase the excitatory processes. Indeed strong pressure on the paw of our morphinized dogs in which the extensor digitorum communis longus was tonically contracted, increased that contraction (fig. 73 at δ). Weak impulses, however, are not able to increase the kinetic energy of the molecular movements responsible for the excitation, which already have a high value. On the other hand, they are able to increase the feebly developed inhibitory process by so much that excitation is decreased or, in suitable cases even suppressed. Comparing the effect of weak stimulation on the quiescent and on the active ganglion cell, one finds that in either case this stimulation increases to a higher degree those processes which at the moment are less developed—i.e., excitation in the quiescent ganglion cell and inhibition in the active ganglion cell. Thus in either case the existing state of the cell is abolished and replaced by the opposite one. These considerations do not, of course, furnish a theory of central innervation, but only some material for such a theory. Whatever shape that theory takes, it will have to reckon with the facts which we have reported. The further development of a theory will largely depend on our progress in the understanding and evaluation of inhibitory processes.

Chapter VIII

CORTICO-CORTICAL CONNECTIONS

Warren Sturgis McCulloch, M.D.

Professor of Psychiatry
University of Illinois College of Medicine
Chicago

OUTLINE OF CHAPTER VIII

Cortico-Cortical Connections

Acknowledgment

THE PORTION of the cortex to be described is neither an anatomical nor a functional unit. Anatomically, it comprises a large part of the frontal lobe but omits the more anterior portion. Functionally, it includes only about half of that portion of the cortex whose strychninization yields somatic sensation (i.e., the sensory cortex of Dusser de Barenne) and, in addition, cortex anterior, medial, and inferior to it. Yet the selected portion has, as the title implies, one property common to all its diverse constituents, adequate electrical stimulation anywhere within it is followed by an alteration of tension in some muscles; what alteration and which muscles depends upon the site and type of electrical stimulation. As appears in Chapter IX this procedure has been so thoroughly investigated that it now serves to identify each of the principal constituents of this portion of the cortex, and to subdivide several of these in monkey, chimpanzee, and man. Hence it suffices as a criterion for identifying homologous areas. This is of importance to the neurologist or neurosurgeon who wishes to draw inferences concerning man from those experiments on monkey and chimpanzee summarized in this chapter

When a map of this portion of the cortex is made to show which muscles respond to minimum adequate electrical stimulation at each motor focus, it is at once apparent that all but two of the constituent areas exercise discrete control over specific groups of muscles. Thus there is an easy method of establishing, in this portion of the cortex, that somatotopic subdivision which will be elaborated presently.

If on the map described above are indicated the type and threshold of adequate electrical stimulation and the type and complexity of muscular responses, it can be seen that every constituent of this portion of the cortex has some defining characteristics dependent upon the concentration, caliber, and course of its efferents. The constituents so distinguished correspond to those cytoarchtectonic areas described histologically in Chapter II, except that in monkey and chimpanzee we must distinguish two areas—herein called 4q and 4r—which lack in these animals those cytoarchitectonic differentiations serving to distinguish areas 4γ and 4a in man. No two of these areas have the same intra- and inter-areal cortico-cortical connections. Figure 79 shows the entire region under discussion—in monkey (a), chimpanzee (b), and man (c).

SOMATOTOPIC SUBDIVISION

The anterior part of the central sector is motor to most somatic muscles. It consists in the monkey and chimpanzee of areas 4q, 4r, 4s, 6, and 44. In

all of these except 4s and 44 it is possible by appropriate stimulation to distinguish major subdivisions for leg, arm, and face, which are separated by narrow regions for the trunk and neck respectively. By other means these subdivisions can be identified in the postcentral portion of the central sector. As shown in Chapter IV, each of these somatotopic subdivisions receives impulses from the lateral thalamic nuclei mediating sensation of the corresponding portion of the soma. Moreover, each of these subdivisions sends impulses back to the corresponding thalamic nucleus or nuclei.
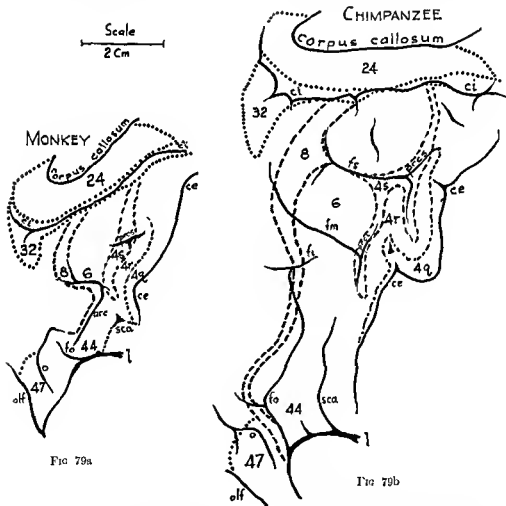
Fig 79—Maps of the precentral motor cortex of the monkey, chimpanzee, and man, drawn to the same scale. To show continuity of the cortex, the area is unrolled medial aspect appears inverted above, lateral aspect, center; orbital aspect, below For significance of numbers, see text.
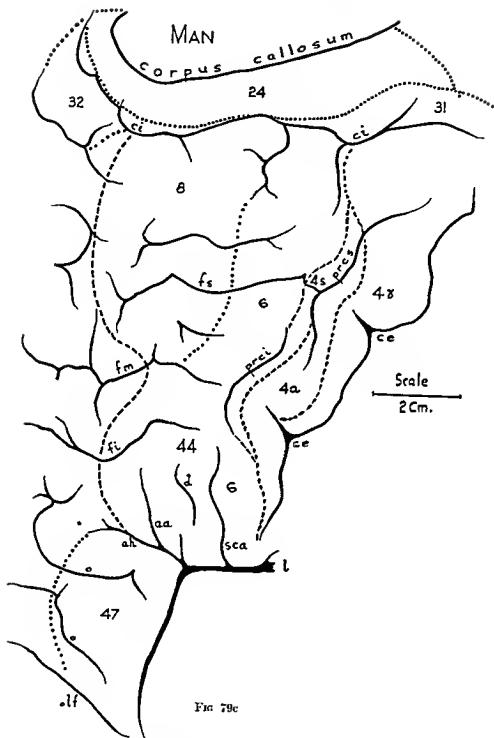
Fig 79c

(For explanation, see preceding page.)

This is schematized in fig 80. In 1916 and 1924 Dusser de Barenne and Sager showed that in cat and monkey excitation of each of these "sensory" lateral thalamic nuclei, either directly, by local strychninization within it or indirectly, by local strychninization within the corresponding subdivision of the sensory cortex, results in the clinical manifestations of paraesthesia, hyperalgesia, and paralgesia of the corresponding parts of the soma.
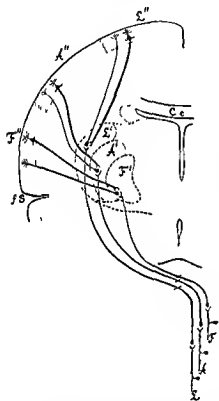
Fig 80—Connections of sensory cortex and lateral sensory thalamic nuclei as revealed by strychnine and electrical record

Although the monkey refers the sensations bilaterally, and more acutely to distal than to proximal portions, no other part of the body is involved unless the strychnine crosses the boundary between somatotopic subdivisions of the sensory cortex or invades lateral thalamic nuclei belonging to more than one subdivision. The importance of this in understanding sensation will appear later. It is described here to indicate that the sensory as well as the motor functions of areas 4q, 4r, and 6 show sharply delineated somatotopic localization.

While adequate threshold stimulation of any particular "motor" focus elicits a unique muscular response, there is an interplay of excitation between any two motor foci belonging to any one subdivision. Except when the interval between excitations is too long, or the motor responses are antagonistic, this interplay is such as to produce what has been called "secondary facilitation"—a term used to describe either of two different phenomena: if two points are selected such that excitation of the first point, *a*, evokes a motor response, *A*; and excitation of the second point, *b*, evokes *B*; and if *a* and *b* belong to the same subdivision and if *A* and *B* are not antagonistic, then appropriately timed successive stimulation of *a* and *b* will cause either (1) a repetition of *A* when *b* is stimulated, or (2) an exaggeration of the response *B*. The first of these types of "secondary facilitation" (*ab-A*) can be obtained even when the point subsequently stimulated lies in certain regions of the sensory cortex from which no primary response can be elicited. This (*ab-A*) has been employed by many observers to obtain

motor responses from the postcentral sensory cortex. It may involve cortico-cortical connections but depends chiefly upon excitation persisting in the subcortical structures affected by the first stimulation, for *b-A* can be demonstrated after severance of all cortico-cortical connections between *a* and *b*. It is therefore not surprising that *ab-A* is more easily elicited if both points lie in the same subdivision, for these must project to the same or closely related portions of the spinal cord.

Figure 81 shows the second type of facilitation. This second type of "secondary facilitation" (*ab-B*) can be elicited even if the point antecedently stimulated yields no motor response. It (*ab-B*) is invariably associated with an electrical change in the cortex at *b* (the "facilitated" focus), and *ab-B* fails when all cortico-cortical connections of *a* and *b* are severed. The response *ab-B* is elicited most regularly at a somewhat longer interval than *ab-A*, and *ab-B* can be demonstrated regularly when *a* exhibits extinction of motor response. Finally, as will appear later, there is reason to believe that the cortico-cortical connections from area 6 to area 4 are large and numerous, while in the reverse direction, from area 4 to area 6, they are wanting; and in this case, if *a* is in area 4 and *b* in area 6, only *ab-A* appears, whereas if *a* lies in area 6 and *b* in area 4, only *ab-B* has ever been described. Thus the occurrence of *ab-B* can be taken as evidence of corticocortical connections. In the monkey's areas 4q and 4r, *ab-B* can be demonstrated from any point to any other point, provided *a* and *b* lie in one and the same subdivision, however remote, but not if *a* lies in one subdivision and *b* in another, although *a* and *b* be separated by only one or two millimeters to prevent spread of the stimulating current across the boundary. These findings are exemplified in fig. 81. They indicate a lack of corticocortical connections between the portions of areas 4q and 4r belonging to different subdivisions. This is true of the chimpanzee's as well as of the monkey's cortex.

Fig. 81.—Oct. 27, 1936. *Macaca mulatta.* Dial narcosis. This figure shows the existence of secondary facilitation at *A* from *a*, 8 mm apart, and the absence of facilitation across the functional boundary between the leg and arm subdivisions, although *A* and *L* are only 3 mm apart.

The foregoing findings are all obscured by any procedure which produces the conditions for self-sustained electrical after-discharge. Thus chloralose anaesthesia, stimulation by frequent long electrical pulses, and all cortical insults or other injuries likely to induce convulsions must be avoided. While these self-sustained disturbances of the cortex are propagated over cortico-cortical fiber systems, they are not restricted to these paths but affect contiguous areas of the cortex, eventually inducing the same disturbances in them, even when they are functionally disparate and even after section of the underlying white matter. They may spread with relatively great speed, say 25 cm. per second, involve the entire cortex, become synchronous, and persist for half an hour. This spread occurs with a velocity to be expected from repeated synaptic relay. Walter Pitts' theory of such spread in a randomly connected net makes its velocity depend upon the time required for summation at a given point to reach threshold, and this harmonizes with the finding that weak strychninization of an area causes the wave to traverse it more rapidly. We would, therefore, attribute this spread to those diffuse connections known histologically as the felt work of the cortex.

To avoid this difficulty, to obtain long and even anaesthesia and electrical activity of the cortex resembling normal sleep with relatively little

Toes
Ankle
Knee
Hip
Shoulder   Thumb
Elbow   Neck
Wrist   Pinna
Fm Digitus Upper face
minimus   Mouth
E Digits 3 & 4 Vocalization
D Digitus
indicis

Fig 82

LEGEND
△ OCULI CONTRALATERAL
▲ OCULI IPSILATERAL
□ OCULI CONTRA
   WITH PUPILLARY DILAT.
■ LACRIMATION
▽ ARM BY FACILITATION

disturbance by afferent impulses, narcosis was obtained by injection of .35 to .45 cc. per kg. body weight of Dial, half the dose given intraperitoneally and half intramuscularly. Except when specifically stated to have been under chloralose, all the following findings were obtained under light or moderate Dial narcosis. The motor responses obtained from the convexity of the cerebral cortex of the chimpanzee are shown in fig. 82.

Under this anaesthesia it is possible to map an eye field frontal to area 6 of the sensory cortex. From it, both ipsilateral and contralateral conjugate deviations of the eyes, with and without pupillary changes and lacrimation, have been elicited, as indicated in fig. 82. This is called area 8. In both the monkey and chimpanzee it begins about one millimeter dorsal to the sulcus callosomarginalis as a narrow band running dorsally and slightly forward at the upper margin of the hemisphere. Thence it descends laterally and widens to the level of the superior frontal sulcus; then narrows and sweeps anteriorly to the inferior margin of the lateral aspect, where it turns medially and occipitally to disappear between the frontal and temporal lobes, but continues onto the insula.

On the orbital surface frontal and medial to area 8 lies area 47, known as the area orbitalis agranularis, stimulation of which yields cessation of respiration in inspiration with the vocal cords abducted. Walker, evidently influenced by Brodmann's figure for the lemur or hapale, has called this area 13.

Finally, on the medial surface, the frontal portion of the gyrus cinguli is occupied by area 24 which extends from the corpus callosum to within a few millimeters of the sulcus callosomarginalis. Stimulation of this area induces changes in somatic muscular activity comparable to those elicitable from both areas 8 and 4s which will be considered later.

Area 24 is separated from the somatic motor field and from the eye field by a narrow strip of cortex, area 32, which, like the remaining portions of the frontal lobe, has failed to yield motor responses.

AREAL SUBDIVISION

Within this region, the subdivisions represented by the functionally defined areas 8, 47, and 24 correspond to cytoarchitectonic entities; whereas in the central sector proper each somatotopic subdivision includes some portion of each of the principal cytoarchitectonic subdivisions. These latter can be distinguished by stimulation. Area 4q begins in and extends forward from the central sulcus as a band, wide in the leg subdivision and tapering to a point in the face subdivision. It is characterized by the elicitation of motor responses which are highly discrete and occur following relatively

weak stimulation Area 4r, lying immediately adjacent to this throughout its length, requires almost twice the strength of stimulation to produce a motor response, but the response is also discrete Anterior and adjacent to area 4r lies area 4s This is a narrow band of cortex, stimulation of which leads to a relaxation of existing muscular tension, interruption of an existing after-discharge produced by stimulation of other cortical foci, and, as shown in fig. 83, a suppression of motor response to stimulation of any focus of area 4q or area 4r—an effect having a latency of about four minutes and usually unrepeatable for three-quarters of an hour. This area was first described in the macacus rhesus monkey by Marion Hines in 1936, who showed that its ablation resulted in the development of spasticity. The details of the microscopic characteristics of these areas are to be found in Chapter II.

Fig 83—Sept 27, 1938 *Macaca mulatta* Dial Electrical monopolar stimulation (Thyratron) of A4 focus once every minute (5 sec -0 6 Γ -40 per sec -V D 1299) Extension of wrist Electrical stimulation of A6 focus gives no suppression Electrical stimulation of A4s focus (6 sec -1 Γ -40 per sec -V D 7000) gives suppression Time line = 20 sec.

Anterior to area 4s, and extending below it, lie areas 6 and 44 Excitation of areas 6 and 44 requires slightly stronger stimulation than 4r, or, more specifically, longer electrical pulses, to yield motor responses, and these are apt to involve a larger number of muscles and more proximal groups Secondary facilitation of the first type (*ab-A*) occurs readily from any focus of area 4q or 4r to any focus of area 6 of the same subdivision and, by moving the electrode by small steps, can be followed for a considerable distance into area 6 of any adjacent subdivision in the chimpanzee—and even to all parts of area 6 in the monkey. For reasons stated above, this indicates the ramification of fibers descending from area 6. Secondary facilitation of the second type (*ab-B*) can be demonstrated more readily from area 6 to areas 4q and 4r if the first stimulation occurs in that part of area 6 which yields primary responses belonging to the subdivision containing the focus of area 4q or 4r subsequently stimulated It can occasionally be demonstrated if the foci lie in different somatotopic subdivisions, but no evidence is available to show that this is mediated by

those cortico-cortical fibers whose existence is demonstrable by other means.

To elicit any response from area 8, prolonged stimulation is required, and the motor and glandular responses are slow to appear and slower to disappear On the other hand, the following three phenomena can be observed: (1) relaxation of existing muscular contractions, (2) holding in abeyance of motor after-discharge—both (1) and (2) appear and disappear promptly—and (3) suppression of motor response to stimulation of any motor focus of the sensory cortex.

These three phenomena can all be elicited powerfully by stimulation of area 24. Thus there are in the region under discussion three areas, 4s, 8, and 24, which will hereafter be referred to as suppressor areas

Area 47, lying antero-medial to area 8 on the orbital surface, yields its muscular response to stimuli resembling those required by area 6.

All motor responses depend necessarily on descending systems, which will be found described in other chapters, notably Chapters V and VI Areas 4q, 4r, 6, and 44 certainly contribute largely to the descending systems of the internal capsule and the pyramids On the other hand, little, if anything, is known of the motor projection of area 47. Finally, only by local strychninization of the cortex and recording from the corpus striatum have the systems descending to these structures been mapped. Thus, the region under consideration has been shown to project corticotopically; that is, cytoarchitectural areas rather than somatotopic subdivisions are seen to be represented in the projection In detail these projections are as follows areas 4s, 8, and 24 project to the nucleus caudatus (as do areas 2, and probably 19, both of which are also suppressor areas). Area 6 projects to the putamen and to the external segment of the globus pallidus, and areas 4q and 4r to the putamen only Nothing is known concerning any possible projection from area 44 to the basal ganglia. The obvious scheme seems to be that suppressor areas project to the nucleus caudatus, and motor areas of the sensory cortex project to the putamen and globus pallidus, pars externa. All these connections are schematized in fig 84, which indicates approximately the general portion of the nucleus caudatus to which the projection occurs. At this point it must be stated that while all suppressor areas project to the nucleus caudatus, even large lesions of the nucleus caudatus do not prevent suppression of motor response—say from area 4s. This is the more important because suppression of motor response has been shown to depend on fibers from these cortical areas descending to the bulbar reticular formation whose excitation is capable of stopping all muscular contraction; and because another suppression (suppression of electrical activity of the cortex, to be described later) does depend on and is mediated

by the nucleus caudatus. It has been shown that the caput nuclei caudati and the cauda, the putamen, the globus pallidus, the substantia nigra, and the cerebellum are severally not necessary to this suppression This has been proved only in the monkey. It was accomplished by a series of experiments in which one or another of these structures was destroyed and the suppression of motor response demonstrated within the following eight hours. It can be stated conclusively that the suppression of electrical activity of area 4 by stimulation of area 4s is not necessary to the suppression of motor response to stimulation of area 4 by antecedent stimulation of 4s, because the latter can be demonstrated when the former is prevented by
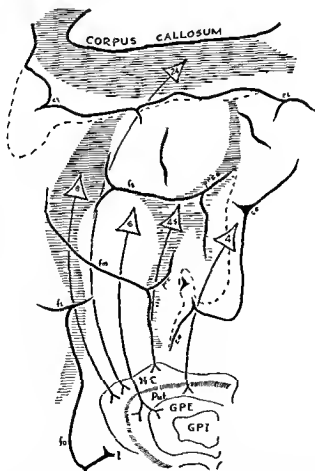
FIG 84—Projections from the precentral motor cortex to the corpus striatum in the chimpanzee as revealed by cortical strychninzation and recording of electrical activity in the corpus striatum

a lesion of the nucleus caudatus. The suppression of electrical activity of the sensory cortex has been shown to depend on impulses from any of the suppressor areas reaching the nucleus caudatus and thence indirectly interrupting in the ventrolateral nuclei of the thalamus that regular rhythmic oscillation of voltages between sensory cortex and thalamus without which there are no ordinary "spontaneous" electrical waves of the sensory cortex.

EVIDENCE FROM PHYSIOLOGICAL
NEURONOGRAPHY

The foregoing was intended to familiarize the reader with those criteria by which one can rapidly outline in any one experiment on a living brain those somatotopic subdivisions and cytoarchitectonic areas whose connections form the subject of this chapter. As the author has had no experience with either histological or histopathological techniques he can only refer the reader to Chapters II, IV, V, and VI, which include the principal evidence concerning these connections as revealed anatomically in the dead brain. The evidence on which the present chapter rests was produced by what Dusser de Barenne has christened "Physiological Neuronography." His life's work has demonstrated that strychnine locally applied acts only where synapses are present on neurons and causes disturbances which are propagated only in the direction of normal conduction—not antidromically. These disturbances appear in records of electrical activity as large, sudden voltages which can be recorded at the site of strychninization and from all regions to which the strychninized neurons send axons or collaterals. At the site of strychninization these sudden transient voltages are many times greater than the ordinary spontaneous activity of the cortex. Cathode ray studies in which the intensity of the spot is made proportional to the first derivative of its displacement but the intensification is slightly delayed, indicate that these disturbances are composed of *almost* synchronous discharges of many cells which, together, produce the observed spikes in the record of the voltage. The size of the spike in any other place to which the disturbance is propagated must be determined by the number and synchronicity of the axonal disturbances reaching that place from the cells fired synchronously at the site of strychninization. Under the conditions of the experiments the author has time and again sought for such spikes at regions to reach which the disturbance would have to pass synapses. He has found none. Instead there have appeared only belated low voltage long waves in the record. These are presumably the delayed and temporally dispersed consequences of the pre-synaptic spikes.

Three considerations make it impossible to state exactly the velocity of propagation of the strychnine spikes: first, the length of the axon cannot be readily determined, but it is always safe to assume that it is at least as long as the separation of two cortical "points," at one of which it arises and at the other of which it terminates; second, these "points" are relatively large, for even with strychninization of only one square millimeter the area of primary spiking is about three millimeters in diameter and the spread of the voltage in the receiving "point" is of at least an equal area; third, and most important, the strychnine spike is not a completely synchronous disturbance but spreads in known ways through the thickness of the cortex. Even so, it is possible to form some estimate of the rate of propagation. Cathode ray determinations indicate a velocity of about 50 meters per second if the initial surface positive wave at the site of strychninization be taken as the time of origin and the beginning of the same wave in the recipient point be taken as the time of termination and the distance is the straight line between the centers of the areas. This figure for the velocity of propagation is probably of the right order of magnitude, and it is probably safe to assume that the maximum velocity is not greater than 100 or less than 10 meters per second. In general, higher velocities were calculated when the points were far apart than when they were near together, but it was not certain whether these differences were due to the difficulty in identifying the corresponding times in the two strychnine spikes or whether they were due to either smaller caliber of shorter axons or the failure to take into account the more circuitous path of short "U" fibers. In any case, the time of transit alone does not preclude the possibility of transsynaptic components. However, there are several other considerations that do so. In the first place, if one undercuts the entire sensory cortex by a lesion immediately external to the corpus striatum the distribution of the distant spikes remains the same. If one then strychninizes the second temporal convolution of one hemisphere he can record the spike from the symmetrical focus, although this produces no spike in any other part of the cortex. The first observation indicates that if relaying occurs it must be in the cortex, and the second observation shows no area of the cortex in which relaying could occur. Thus together they exclude "relaying" of the strychnine spike as a necessary factor in propagation, and so strengthen the negative evidence noted above. Finally, it is possible to locate three widely separated cortical points such that strychninization of *A* causes a spike at *B* and strychninization of *B* causes a spike at *C*, yet strychninization of *A*, while it may yield a much belated low wave at *C*, never results in a spike at *C*.
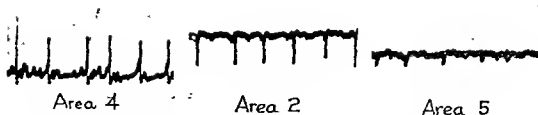
FIG 85 —Macaque Dial anaesthesia Strychninization of area 4 Cathode ray oscillogram
6 minutes later, showing typical strychnine spikes in areas 4 and 2 and small spikes in area 5

For all of the foregoing reasons it is clear that strychninization of any cortical area causes a synchronous disturbance of cells in the area strychninized, and that this disturbance can be found in all other cortical areas to which it sends a sufficient number of axons In this manner local strychninization can be used to map the axonal distribution of cells situated in any area; but it must be remembered that if either the cells of origin for a given axonal distribution are too few or too scattered, or the axonal endings in the field in question are too few or too scattered, the method must fail to disclose them Hence it should be considered that in the following description positive findings are conclusive but not all-inclusive. They indicate the principal and compact cortico-cortical connections. To make this clearer it is well to contrast one experiment under chloralose with the corresponding experiment under Dial. If one strychninizes one square millimeter of arm area in the monkey under Dial, one obtains strychnine spikes in all parts of arm area 4 and in the postcentral arm areas (shown in fig. 85), but not in area 6 or any parts of the leg or face subdivisions. If one now circumthermocoagulates the entire thickness of the cortex about the focus strychninized, the distribution of the strychnine spike remains unaltered. It follows from this and the experiment in which the entire cortex was separated from all subcortical structures that the path of these disturbances is downward into the white matter and through it to the postcentral areas affected. Rosenblueth and Cannon (1942) showed that under chloralose the strychnine spike described above is complicated by the presence of a much slower disturbance which is also much more slowly propagated. and that this slower disturbance sweeps across all boundaries into area 6. into the adjacent leg and face subdivisions, into all parts of the post-central cortex and even into unrelated regions—its amplitude decreasing as it travels. If now this strychninized focus is circumthermocoagulated. the slow wave disappears. leaving only the strychnine spikes distributed as they are under Dial narcosis. No one doubts the existence of horizontal

axons in the substance of the cortex, and it may be through these that the slower disturbance seen under chloralose is propagated Under Dial—and also without narcosis—the method of Physiological Neuronography fails to indicate their presence. If these provisos are kept in mind no false interpretations are likely to be made of the following findings It must also be remembered that to procure comparable results the cortex must be exposed with care to insure adequate blood supply and to avoid unnecessary injuries to the pia-arachnoid membrane, and that the surface must be almost dry at the time when and place where a few square millimeters of
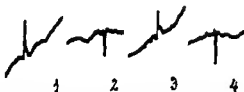
Fig 86—Monkey (*Macaca mulatta*) Dial narcosis Strychnine spikes from postcentral face area 1, from surface (20″ after strychnization), 2, from depth of 1 35 mm (1′25″ after strychnization), 3, again from surface (2′10″ after strychnization), 4, again from depth of 1 35 mm (2′40″ after strychnization)

filter paper moistened with a saturated solution of strychnine sulphate are applied It needs scarcely be stated that the placing of electrodes and their connection will affect the wave-form recorded, and both must therefore always be so arranged as to permit reference of the events recorded to those localities in which they occur. To this end, so-called "triangulation" with several amplifiers having differential input stages is highly desirable.

The results are reported under three general captions: first, the generation and vertical movement of the strychnine spike at its site of origin; second, the distribution of the strychnine spike within the area strychninized; third, the distribution to remote portions of the cortex.

At the Site of Strychninization

When a square millimeter of cortex is strychninized the minute area of surface becomes negative to any remote region, and after less than half a minute there appear on this negativity small negative spikes which steadily increase in amplitude. If at this time an electrode, insulated except at the tip, is plunged into the lower layers of the cortex, these disturbances are recorded as small positive spikes. This is shown in fig. 86. Such wave-forms—surface-negative, depth-positive—are characteristic of disturbances of the superficial layers of the cortex. This is confirmed by Adrian's findings in 1936. They are all that is recorded until the strychnine

has had time to reach and excite the deeper layers. When this happens the surface-negative wave is preceded by a surface-positive wave. Figure 87 shows this development of the strychnine spike. By the method which Dusser de Barenne called "Laminar Thermocoagulation" one can kill the outer layers of the cortex, leaving the deeper layers functional. Figure 88 shows the result of such a laminar thermocoagulation. If this is done when there are only surface-negative waves, no spike remains; whereas if it is done when the wave has become biphasic the initial surface-positive phase remains but the subsequent surface-negative phase is gone. This is
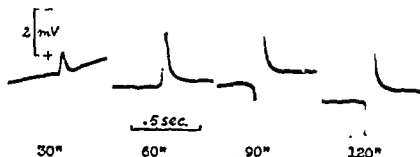
Fig 87—Macaque Dial Local strychnization of an arm 4 focus Record shows surface potential at the number of seconds after strychnization which are indicated in the diagram

shown in fig. 89. If the electrode is now plunged into the deeper layers only the depth-negative—i e the surface-positive wave—is recorded. Therefore this surface-positive wave has to be attributed to activity in the depth. If a similar procedure were followed on peripheral nerve, it would be called "rendering a lead monophasic" and one would expect that if the nerve lived long enough the monophasicity of the lead would disappear, and this is what happens in the case of the cortex. Within a matter of hours (five to eight) the diphasicity returns

There is a second procedure, not hitherto described, invented by Mr. Craig Goodwin, of the University of Illinois, and tried out by Dr. Hugh Garol and Mr. John Hamilton for thermocoagulating the deeper layers, leaving the superficial layers of the cortex intact. It depends upon a high frequency current administered to the area through a large chilled electrode. Great difficulty was experienced in obtaining lesions of the desired form and depth, and it may be a long time before the exact conditions for so doing can be prescribed. However, Mr. Goodwin, with Dr. Roseman and Dr. Silveira, has succeeded unexpectedly upon several occasions, and although adequate histological controls are not yet available, their experiments have shown that if the deeper layers are thermocoagulated and any of the superficial layers remain, these layers give only surface-negative-
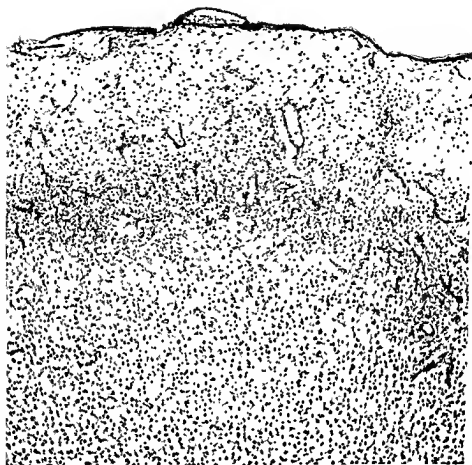
FIG 88—Section of the motor cortex of area 4, stained by Nissl's method showing destruction of the layers external to the layer of large and giant pyramidal cells. The animal was killed seven days after local thermocoagulation which was at circa 75 degrees for 3 seconds

depth-positive potentials upon local strychninization. Again, the diphasicity returns in some five to eight hours.

Thus these two sets of experiments supplement each other and indicate that, as in peripheral nerve, the disturbance is negative where it occurs and is associated with a positivity at a measured distance of even less than one millimeter.

When the strychnine spike is fully developed in a lightly narcotized cortex the form is triphasic—initial surface-positive, subsequent surface-negative, and final surface-positive, the last being a longer and more widespread disturbance.
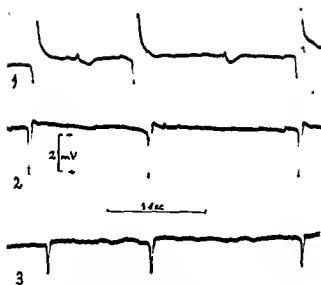
Fig. 89.—Macaque. Dial 1. Strychnine-spikes from A6 focus. 2, same, 5 minutes after thermocoagulation of 3 outer layers (TC, 70°C −3″). 3, same, 4 minutes after subsequent damage to fourth layer (TC, 70°C −3½″).

Thermocoagulation which abolishes the surface-negative phase in no way affects the propagation of the strychnine spike to other cortical points. This is not surprising inasmuch as the early monophasic surface negativity is never associated with propagation. Moreover, when propagation occurs it must, from time studies of the propagation, arise from the initial positive wave under all ordinary circumstances.

At the present time Dr. Silveira is studying (by laminar thermocoagulation, strychninization, and electrical recording) the layers of the cortex giving rise to the cortico-cortical connections. In that undertaking he has already been able to indicate that, at least from certain areas, the efferent impulses continue to go to other cortical areas until the thermocoagulation is sufficiently deep to abolish the surface-positive phase.

Finally, Dr. Silveira has shown that if the most superficial layers of the cortex have been thermocoagulated several days prior to strychninization, the propagation can occur from the second, more widespread, surface-positive phase.

These as yet unpublished studies so complete the picture as to permit the following description of the cortical events under the point of application of the strychnine at the time when the strychnine spike is fully developed. First, there is a discharge of cells in the deeper layers of the cortex

Area 47: Strychninization in this area causes firing within it which is distributed in an antero-posterior band little wider than the strychninization.

Area 24: Strychninization here gives the same extremely local disturbance seen in areas 4s and 8

Strychninization in the narrow band of cortex separating area 24 from area 8 causes firing throughout that band which Brodmann, in his figure for the monkey, misses all but its anterior end which he there labels area 32, whereas in his figure for man he divides it into two parts: areas 31 and 32. This corresponds most nearly to the areas disclosed in the chimpanzee. Mauss, in his figure of the monkey, calls it area 31 and uses the symbol T. This corresponds to the area as found in the monkey, except for the anterior end which is more nearly like Brodmann's 32 in the monkey. Von Economo and Koskinas so subdivide this area in man (fig. 3b, p. 12) that it is impossible to homologize it with the areas disclosed in these studies. Thus Brodmann's figure for man (fig. 2b, p. 11)—areas 31 and 32—forms the best guide. This area is important not merely because it lies to such an extent within the "motor" area without being "motor," but because of its afferent cortico-cortical connections which are unique.

Finally, there exists area 3 which, in the face subdivision, becomes precentral. Motor responses have been elicited from this region by most observers. They involve the mouth, tongue, pharynx, and larynx, and can be obtained even after subpial resection of areas 4 and 6. However, this region has been relatively little studied by this method and its boundaries are so ill defined in these experiments that it is scarcely worth reporting. It has, in these studies, always been regarded as belonging to the postcentral region. To

Fig 91a

Fig 91.—Maps indicate areas of sensory and adjacent cortex, distinguishable by physiological neuronography, in monkey (*Macaca mulatta*), *a*, and chimpanzee (*Pan satyrus*), *b* Below are diagrams indicating maximal axonal field disclosed by repeated strychninizations in area marked △. Horizontal dashes indicate suppression of electrical activity; Y indicates area fired, ce refers to central sulcus, double vertical lines indicate anterior and posterior borders of sensory cortex. For significance of numbers, see text

work out its detailed organization would probably require an exorbitant number of experiments, for its boundaries lack anatomical landmarks. What little is known of it is indicated in fig. 91a. It certainly fires itself within a somatotopic subdivision, but the attempts to disclose it in the depths of the central sulcus have not yielded sufficiently good preparations to make it certain that firing is restricted to the field, for that could only be established by a large number of negative instances.

Inter-Areal Cortico-Cortical Connections

The inter-areal connections by cortico-cortical axons can best be divided into those which are afferent to and those which are efferent from the area in question. The commissural connections are most commonly symmetrical, or homoiotopic, but the exceptions are important and therefore must also be specified. They will be presented separately, to avoid possible confusion or unnecessary repetition. One other consideration enters here. Since one is forced to assign symbols to areas of the postcentral cortex because these send afferents to the "motor" area, and because these postcentral areas lack the criterion of well-known motor specificity as a basis of homology, it has seemed best for present purposes to use for them the symbols Brodmann has used for man. Certain of the areas are easily identified, notably 1 and 2, whereas the identification of area 5 is at best tentative, and of area 7, questionable. However, in the monkey the projection of all of these areas to the ventrolateral thalamic nuclei in somatotopic fashion establishes their sensory significance. The cytoarchitectonic map of the chimpanzee is wanting, and area 7 of man fails to appear below the sulcus intraparietalis. In its stead there appear areas 39 and 40—on the angular and supramarginal gyri, respectively. In the chimpanzee this region projects to the pulvinar instead of to the lateral, sensory, thalamic nuclei. What has become of the large area 7 in the arm and face subdivisions of the sensory cortex of the monkey (see fig. 91a) is unknown. It does not seem likely that area 7 crossed the visuosensory band β of Elliot Smith to lie solely in the superior parietal lobule, but the other alternative —namely, that as it developed into areas 39 and 40 it altered its thalamic connections from the lateral nuclei to the pulvinar, seems equally unlikely. However, since the description is to be based on the chimpanzee, one is compelled to regard these areas as 39 and 40—not as area 7. Figure 91b is best used as a guide to the following statements.

Homolateral Inter-Areal Connections

Area 4q. Receives cortico-cortical impulses from areas 4r, 6, 1, 5, and in the leg subdivision from area 7; sends impulses to areas 1 and 5.

Area 4r: Receives impulses from areas 6 and 1, and in the arm subdivision from what is here called area 40; sends impulses to areas 4s, 4q, and what is here called area 39.

Area 4s: Receives impulses from areas 6, 4r, 1, and 39, but sends impulses only to area 32. The last confirms the anatomical finding of a tract running from 4s into the vicinity of the sulcus calloso-marginalis described in Chapter IV.

Area 6: No cortico-cortical afferents have been discovered. In the leg subdivision and in the arm subdivision, area 6 sends impulses to both leg and arm subdivisions of areas 4s, 4r, 4q, 1, and 5, into area 39 from the arm subdivision, and into the posterior part of the superior parietal lobule from the leg subdivision. In the face subdivision area 6 sends impulses to the face subdivision, but the detailed evidence in the chimpanzee is inadequate for a full statement. The reader is referred to fig. 91a for the analysis in the monkey.

Area 44: Receives impulses from area 6 and from supratemporal plane.

Area 8: No cortico-cortical afferents have been found, and no cortical efferents except to area 32 and, from one part, just anterior to arm area 6, to area 18.

Area 47: No cortico-cortical afferents have been discovered. Its cortical efferent systems run, via the fasciculus uncinatus, to area 38, which is the temporo-polar area. (In the monkey it receives them thence.)

Area 24: No cortico-cortical afferents have appeared, but they have not been sought exhaustively. Its cortico-cortical efferent fibers run into areas 31 and 32.

Areas 31 and 32: These areas receive impulses from areas 19, 2, 4s, 8, and 24—i.e., from all suppressor areas hitherto found. If areas 31 and 32 be considered two, each is afferent and efferent to the other, but it seems more sensible, on the basis of myeloarchitecture, to consider it as one area, as Mauss did in the monkey.

Commissural Cortico-Cortical Connections

It seems fairly certain that all the interhemispherical cortico-cortical connections of the region of cortex under consideration pass through the corpus callosum, not through the anterior commissure. The only possible exception involves area 47, on whose interhemispherical connections neither the work reported here nor any other known to the author has thrown any light. The convexity of the hemisphere has been thoroughly investigated by three methods; first, by lesions and Marchi stains (Chapters IV and V); second, by electrical stimulation and records of electrical response; third, by strychninization and records of electrical response. The first method has

been most extensively used by Mettler during the years 1935 and 1936. It was he who coined the term "homoiotopic" to cover the type of projection which is most commonly found throughout—namely, the projection from a region on one hemisphere to the corresponding region of the opposite hemisphere. The author is indebted to him for the suggestion of how widely the projections might be scattered, for this led to application of many more electrodes than would otherwise have been thought necessary and, so, to the discovery of several of these projections which would otherwise have been missed. The second method, employed by Curtis and Bard in 1939 and 1940, had already disclosed all the interhemispherical connections of the upper portion of the convexity of the hemisphere which the author and his collaborators later confirmed. The differences between electrical stimulation and strychninization are that the former may excite axonal terminations causing antidromic firing, and that it may excite any fibers subjacent to the stimulating electrode. These differences may account for the author's inability to confirm all of the findings obtained by electrical stimulation. On the other hand, this difference may be due to the large number of cells that must be fired synchronously to produce what was regarded as a strychnine spike on the opposite hemisphere. Be that as it may, the findings, aside from extensions to areas not previously investigated, differ from those of Curtis and Bard only privatively, and it is probably safe to regard the connections reported here as representing the most numerous and concentrated projections rather than as an exhaustive array. On this same score, the reader should remember that less than one-third of the cortex appears on the exposed surface, and that the depths of the sulci were neither strychninized nor recorded. Figure 92 shows the origins of these systems from the convexity of the hemisphere in the monkey (fig. 92a) and chimpanzee (fig. 92b).

Area 4q: Shows callosal connections which are only homoiotopic, the connections being extremely well localized to the exactly symmetrical motor focus Moreover, these connections arise only from the representations of trunk, neck, and lower face—i e , only from motor foci for parts of the soma used almost exclusively bilaterally, not from the foci for movements of the parts used typically otherwise, i.e., feet, hands, and upper face.

Area 4r· The connection is essentially similar to that from 4q.

Area 4s: Sends no interhemispherical connections.

Area 6: All parts of both send homoiotopic and heterotopic connections to most of the sensory cortex of the same somatotopic subdivisions. and in certain instances to points in other subdivisions. In these must be included areas 39 and 40, which, while they are part of the arm subdivision. have been fired from face 6 and leg 6.

Area 8: Sends callosal connections to the contralateral area 18 but

to no other part of the contralateral hemisphere. This tract arises from its posterior margin anterior to arm 6.

Area 47: Not yet investigated.

Area 24: Not yet proved to have any such connections, but they have not been definitely excluded.

Areas 31 and 32: Send homoiotopic connections, but it cannot yet be asserted definitely that no heterotopic connections exist, for the studies do not yet exclude all heterotopic possibilities.

The homoiotopic connections mentioned above necessarily indicate that the areas originating also receive homoiotopic connections, but fail to indicate the reception of heterotopic connections from other areas within and without the area under discussion. Hence the receipt of heterotopic connections are listed below.

Area 4q: Receives interhemispheric homoiotopic connections from area 4q in the same restricted fashion as that in which it sends them. In addition, many parts, if not all, of area 4 receive heterotopic connections from area 6 and from a small portion of the superior parietal lobule lying inside the sulcus postcentralis superior.

Area 4r: Connections are essentially similar to area 4q.

Area 4s: Receives no interhemispherical connection, with the possible exception of one from area 6, which has been found only once.

Area 6: Receives only homoiotopic connections.

Area 44: Only insufficient evidence is available.

Area 8: Receives no discoverable callosal connection of any kind.

Area 47: Not yet investigated.

Area 24: Investigated by strychninization of the opposite medial aspect, and no heterotopic firing has been found.
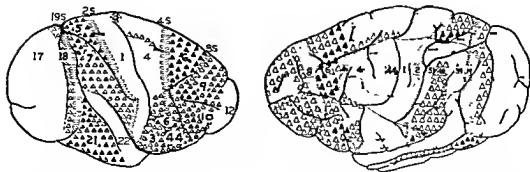
Fig. 92.—Maps of the convexity of the hemisphere, indicating origins of commissural systems, as revealed by physiological neuronography, in monkey (*Macaca mulatta*) 92a (*left*) and chimpanzee (*Pan satyrus*) 92b (*right*) For explanation of numbers, see text. △ = Projection to contralateral hemisphere at symmetrical focus only. ▲ = Projection to contralateral hemisphere at symmetrical and other foci. ◬ = Projection to contralateral hemisphere at symmetrical focus only which remains after section of the corpus callosum

Table III
HOMOLATERAL INTER-AREAL CONNECTIONS

Area Strychninized	Area Recording																
	31-32	24	47	8	6	4s	4r	4q	1	2	5	40	39	19	18	17	44
31-32	A	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	?
24	+	L	0	0	0	0	0	0	0	0	0	0	0	0	0	0	?
47	?	?	R	0	0	0	0	0	0	0	0	0	0	0	0	0	?
8	+	–	–	L	0	0	0	0	0	0	0	0	0	0	+	–	?
6	0	0	?	0	A	+	+	+	+	?	+	0	–	0	0	–	?
4s	+	–	–	–	–	L	–	–	+	–	–	0	–	0	0	0	+
4r	0	0	0	0	0	+	R	+	0	0	0	0	+	0	0	0	+
4q	0	0	0	0	0	+	R	+	+	0	+	0	0	0	0	0	+
1	0	0	0	0	+	+	+	Γ	?	+	0	+	0	0	0	0	?
2	+	–	0	0	0	0	0	0	0	–	0	0	0	0	0	0	?
5	0	0	0	0	0	0	+	+	+	F	0	0	0	0	0	0	?
40	0	0	0	0	0	0	+	0	0	0	Γ	0	0	0	0	0	?
39	0	0	0	0	+	0	0	0	0	0	?	0	+	0	0	0	?
19	+	0	0	0	0	0	0	0	0	0	0	–	R	–	–	–	?
18	0	0	0	0	0	0	0	0	0	0	0	0	+	+	A	+	?
17	0	0	0	0	0	0	0	0	0	0	0	0	0	+	–	L	?
41-42	?	?	?	+	0	0	0	0	0	0	0	+	+	+	?	0	?

Areas 31 and 32: No heterotopic firing has been found.

This extensive statement of the inter-areal connections is recapitulated in Tables III and IV. In these tables ignorance is indicated by ?, definitely established firing by +, and equally well-established lack of firing by 0. The reader is again cautioned that the zero does not mean a lack of all connections but merely a lack of sufficient connections to produce an identifiable disturbance. For this reason it summarizes the major inter-areal connections. In those places which represent strychninization within the area recorded, L indicates strictly local firing; R, firing restricted to a somewhat larger portion of the cortex belonging to the same area and same subdivision; A, firing restricted to the area; F, firing of the whole area within the somatotopic subdivision; —, the suppression of electrical activity, described below; *TNF*, trunk, neck, and face only.

There is a second phenomenon which appears at cortical points remote from the site of strychnine when this is in area 4s, 8, 2, 24, or 19. It has been called "suppression of electrical activity" (see fig. 93). It begins from 4 to 12 minutes after strychninization and more promptly after mechanical or electrical stimulation of these areas. It consists of a diminution, which may amount to disappearance, of electrical activity of the cortex, first in the vicinity of the area strychninized and then at points more remote, requiring some half an hour to reach the most remote parts of the cortex. By

Table IV

CONTRALATERAL INTER-AREAL CONNECTIONS

Area Strychninized	Area Recording															
	31-32	24	47	8	6	4s	4r	4q	1	2	5	40	39	19	18	17
31-32	+	0	?	0	0	0	0	0	0	0	0	0	0	0	0	0
24	-	0	?	-	-	-	-	-	-	-	-	-	-	-	-	-
47	?	?	-	?	?	?	?	?	?	?	?	?	?	?	?	?
8	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-
6	0	0	?	0	+	?	+	+	+	0	+	0	+	0	0	0
4s	-	-	?	-	-	-	-	-	-	-	-	-	-	-	-	-
4r	0	0	?	0	0	0	TNF	0	0	0	0	0	0	0	0	0
4q	0	0	?	0	0	0	0	TNF	0	0	0	0	0	0	0	0
1	0	0	?	0	0	0	0	0	0	0	0	0	0	0	0	0
2	-	-	?	-	-	-	-	-	-	-	-	-	-	-	-	-
5	0	0	?	0	0	0	0	+	+	0	+	0	+	0	0	0
40	0	0	?	0	0	0	0	0	0	0	0	+	0	0	0	0
39	0	0	?	0	0	0	0	0	0	0	0	0	0	0	0	0
19	-	-	?	-	-	-	-	-	-	-	-	-	-	-	-	-
18	-	0	?	0	0	0	0	0	0	0	0	0	0	0	+	0
17	0	0	?	0	0	0	0	0	0	0	0	0	0	0	0	0

this time the nearer areas have re-established activity, first as batches of electric waves whose envelope is fusiform, hence called "spindling," and, later, as normal activity. Figure 93 exemplifies this finding This suppression is mentioned here to emphasize that, although it is a cortical result of cortical activity, it does not depend upon cortico-cortical connections, for
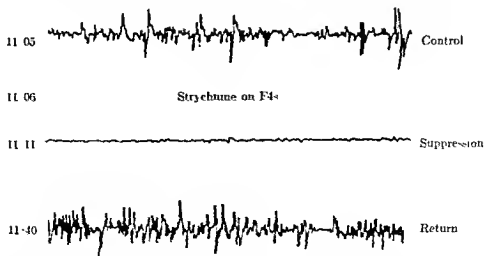
Fig 93—Macaque Dial Example of the suppression of electrical activity of area A4 following strychninization of F4s

nous firing of cortical cells to disclose any of these systems of efferents, provided there is a sufficient concentration of them at the site recorded. By this means it is possible to subdivide the precentral motor cortex into five areas (4q, 4r, 4s, 6 and 44) belonging to and intimately connected with other portions of the sensory cortex. Immediately anterior to it lies area 8 which sends impulses back to area 18—a field which is also "motor" to the eyes. Anterior to this area 8 on the orbital surface this method has revealed area 47 which sends impulses via the fasciculus uncinatus to area 38, capping the temporal pole. Situated within the anterior half of the gyrus cinguli it has disclosed another area which, like areas 4s and 8, sends impulses to the narrow strip of cortex called areas 31 and 32 and has thus established a pathway to the frontal pole—from these and from all other "suppressor" areas. It has, moreover, disclosed localized homoiotopic callosal connections arising and terminating in areas 4q and 4r, but only from and to those portions of these areas which are concerned bilaterally in ordinary movements. From area 6 which, in a sense, is a motor associational area, it has disclosed the widest distribution of callosal connections, homoiotopic and heterotopic. And, finally, it has failed to disclose any such connections from any of the "suppressor" areas except from area 8 to area 18. These are to be regarded as the chief, but not necessarily the only, cortico-cortical connections arising from each of the above areas. Evidence has been adduced to indicate that the interpretation of the normal function of these connections—other than that of interrelating the activity of the areas in question—is still to be determined. Of all the functions normally demonstrable by cortical stimulation, only one type of secondary facilitation and the spread of cortical after-discharge can definitely be referred to these cortico-cortical connections. The rest, facilitation, extinction, and suppression of electrical activity or of motor response to electrical stimulation of the cortex—even the reference of sensation, like the elicitation of motor response—depend on descending systems.

One relation has probably been understated or obscured by details. This is important when one tries to extrapolate from monkey through chimpanzee to man. So long as the size of area strychninized is held constant and homologous cortical areas are strychninized, the total size of areas of response in monkey and in chimpanzee are approximately equal (fig. 90). It is as if the concentration of the cells of origin of these systems remained constant for any given region. This means that with expansion of the cortex one would have to expect just such differences as exist between monkey and chimpanzee—namely, that with increase of surface area there appears a greater differentiation in the sense of a greater specificity of distribution. This, in turn, would lead one to expect still greater specificity in man.

Chapter IX

SOMATIC FUNCTIONS

Margaret A. Kennard, M.D.

Associate Professor of Experimental Surgery
University of Oregon Medical School[1]
Portland

OUTLINE OF CHAPTER IX

Somatic Functions

I. HISTORICAL

II. PRESENT KNOWLEDGE

SOMATIC FUNCTIONS

BECAUSE MOTOR ACTIVITY was the first focal cortical cerebral function to be discovered and because investigations of every kind since 1870 have stemmed from the demonstration by Fritsch and Hitzig that focal cortical stimulation produced focal movement, the somatic functions of the precentral motor area are at once the most obvious and the most difficult to describe. There are 70 years of voluminous literature on the subject which has been approached from innumerable angles. Moreover, in this monograph the chapters of nearly every other author must deal in part with somatic activity, thereby increasing the difficulty of selecting the material and limitations for this chapter. Consequently, it has seemed best to restrict it to two parts as follows: (1) A brief review of the development of the earlier accepted knowledge of the somatic motor functions of the cerebral cortex, with references to the many previous reviews of the same subject. (2) A more detailed discussion of recent and controversial material, emphasizing largely the functional organization of the motor system.

HISTORICAL

During the latter half of the 19th century, investigations of the function of the cerebral cortex were undertaken in many laboratories and hospitals. The earliest significant facts, influencing all later work, were elaborated by Fritsch and Hitzig who first reported in 1870 that movement could be produced by electrical stimulation of the brain of a dog, and by Hughlings Jackson who from clinical observations (1863, 1870, 1875) began to develop the idea that focal epilepsy was the result of a focal lesion in the contralateral cerebral hemisphere. By means of these two methods, and later by use of cortical ablations, all the early knowledge of cortical function was acquired.

Stimulation

Early Investigations—By 1902, Monakow, reporting on the "present status of the question of cortical localization," cited 846 references to previous literature which were largely, although not entirely, concerned with the localization of somatic function within the precentral area. Chief among those investigators of the cortex to use electrical stimulation were Hitzig (summarized in 1904), Schiff (1875), Bubnoff and Heidenhain (1881; cf. Chapter VII), Exner (1881), and Munk (1881) in Germany; Luciani and Tamburini (1879) in Italy; Bochefontaine (1883) in France;

the whole complex of motor units The animal's motor behaviour where the brain-nets are large excels in variety and nicety But it fails to offer anything radically different from that of reflex action elsewhere

I may seem to stress the preoccupation of the brain with muscle Can we stress too much that preoccupation when any path we trace in the brain leads directly or indirectly to muscle? The brain seems a thoroughfare for nerve-action passing on its way to the motor animal It has been remarked that Life's aim is an act, not a thought Today the dictum must be modified to admit that, often, to refrain from an act is no less an act than to commit one, because inhibition is coequally with excitation a nervous activity

Clinical Observations

Area 4—The earliest observations of cortical motor function must have been made clinically; for it was known before the time of Hughlings Jackson that injury to a cerebral hemisphere might modify contralateral motor performance (Fulton, 1938, 1943). Jackson, however, was the first to suggest that focal epileptic attacks might be due to focal lesions in the precentral cortex (1870). Shortly after this time, Jackson (1875), Gowers, (1886-1888), Bastian (1875), and their students elaborated the details of focal attacks from observation of a great number of patients. The relation of conjugate deviation of the eyes to the cortex had been discussed earlier by Prevost (1868) and later in some detail by L. Bard (1904). The bilaterality of cortical function was discussed by Dignat in 1883.

Later, during and after the first World War, the effect of gunshot wounds of the head led Foerster (1926b, 1930) to make detailed observations on focal lesions, not only with regard to the motor system but to sensory functions of all kinds. The complications of epileptic attacks as late effects of injury were described by Foerster and Penfield (1930). Much of this information is now too common a part of the body of clinical knowledge to be thought of as anything but old and accepted fact.

The connection of other areas of the cortex with the motor area whereby motor epilepsy might be initiated elsewhere was elaborated in detail. Recognition by Gowers (1907) of the fact that focal attacks might begin with symptoms other than those of disturbance of the somatic motor system and that these might be caused by lesions elsewhere led to further analysis, and numerous specific symptoms were then related to distant regions of the cortex. Visual and olfactory attacks were associated with the uncinate gyrus, and there are now temporal, occipital, and parietal epileptiform syndromes, signifying paroxysmal irritation of these areas. Excision of irritative foci (Horsley, 1890, 1909; Keen, 1888; Foerster and Penfield, 1930) was the next result of the increased knowledge of localization of function within the cortex.

The interest in focal cerebral signs and their clinical significance led to the elaboration at the end of the last century of a number of diagnostic

signs each labelled with the name of its discoverer, the sign of Babinski (1896) being the best known and most widely used at the moment (Fulton and Keller, 1932a).

Area 6—There is little in the early clinical literature which delimited the functions of area 6 of the motor cortex from either the chaotic unknown frontal pole or the true motor region. area 4 (figs. 2, 95). But with present-day knowledge. earlier clinical descriptions of symptoms can be found which are those of lesions of the rostral portion of the precentral cortex, area 6 of Brodmann (fig 95). or the premotor cortex of Fulton (1934b, 1935).

In 1905, Liepmann described tonic flexion of the hands which appeared with lesions of the frontal lobe. In 1914, Wilson and Walshe published an extensive review of similar cases and cited three of their own with "tonic innervation" of one hand only. The lesion was in the contralateral frontal
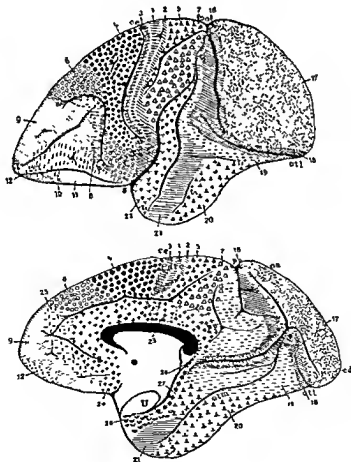
Fig. 95—Cytoarchitectural subdivisions of the cerebral cortex in the monkey (Cercopithecus) After Brodmann (1909)

lobe; the description was that of the symptom later called forced grasping (Adie and Critchley, 1927). Following the first descriptions of aphasia by Broca, apraxia was identified, and a syndrome consisting of aphasia or apraxia, together with tonic innervation and hyperreflexia was associated with lesions of the frontal lobe. This syndrome now is known to be specific to areas 6 and 44, lying just rostral to the true motor area (frontispiece).

There are many early analyses of flaccid and so-called rigid paralyses (Gowers, 1886–1888; Bastian, 1875), but there is nothing mentioned of localizing significance in these symptoms prior to the papers of Fulton and Keller (1932a) and Richter and Hines (1932, 1934).

Involuntary Movements—Horsley, the first to excise a cortical focus for Jacksonian epilepsy, also excised the hand area from a child with athetosis (1890), thereby producing a focal paresis and abolishing the involuntary movements. Later he repeated this on at least three more patients (1909). He seems, from his articles, to have done this because he thought that since in epilepsy the cortex excited a trigger point the same might be true in the case of athetosis or chorea. There is not much discussion of the matter in his papers, and the relation of the motor cortex to the subcortical striate bodies seems to have been forgotten until much later (see Bucy and Buchanan, 1932; Bucy and Case, 1937, discussed in Chapter XV).

Ablation Experiments

The results obtained by stimulation experiments were early supplemented by observations of residual motor performance following ablations from the cortex. The most valuable of these were made on the monkey by Ferrier (1876), Horsley and Schäfer (1888), and Bianchi (1922).

Area 4—From these experiments cortical paresis was analyzed as having the following characteristics: it was transient in the monkey; it affected chiefly the fingers and toes; recovery began in the proximal joints; and there was bilaterality of function (Rothmann, 1907). Biedl (1897) first recorded the fact that after seriatim cortical destruction from two hemispheres, the arm contralateral to the first ablation recovered an additional measure of function immediately after destruction of the second side, due, it has been since thought (Ogden and Franz, 1917–1918), to the necessity for use of the paretic arm in the absence of a useful arm on the opposite side, and in spite of bilateral representation in the cortex.

Ablations in Man—As mentioned above, Keen (1888), Bidwell and Sherrington (1893), and Troje (1894) all made observations on human patients after discrete removals of focal lesions, and later Foerster (1936b) made use of this technique to record systematically the functions of the focal points in the sensorimotor cortex of man.

Rothmann (1907) devised and carried out intricate experiments which were the first to indicate that the Betz cells of area 4 were not exclusively responsible for cortico-spinal innervation The idea that Betz cells were the sole origin of the pyramidal tract had been formulated by the cytoarchitecturally minded and was later investigated and substantiated by Holmes and Page May (1909) Rothmann, however, demonstrated very convincingly by first sectioning one pyramidal tract and later removing the cortical focus for arm from the opposite hemisphere that there was an added deficit in the hand following the second operation. He thus showed the presence of an extrapyramidal system arising from the precentral region. He also produced movement on the side of a pyramidal tract section by stimulation of area 4 on the contralateral side. This work was later confirmed and elaborated by Marshall (1933, 1936) and by Tower (1935, 1940). (See Chapter VI)

Area 6—In the descriptions of monkeys following cortical ablations there is no indication in the early literature of any focal qualities specific to area 6, the premotor area, but there are many symptoms mentioned which can now be assigned to that region Ferrier (1876) described hypomotility and apathy in monkeys after bilateral frontal injury. He quoted Goltz, Hitzig, and Horsley and Schafer as having found the same. Bianchi (1895, 1922) mentioned stereotypy and automatism as part of the effect of cortical ablation. All these symptoms are now considered as related to the regions just rostral to the true motor area 4 which in primates he in area 6 of Brodmann (Fulton, 1933-1934, 1938).

Area 8—Levinsohn (1909) carried out extensive investigations of eye movement following lesions in the region of area 8 as well as in posteentral areas and described accurately the transient conjugate deviation of head and eyes toward the side of the operation when area 8 had been damaged. Monakow (1902, 1914) gives extensive bibliographies of such work up to the time of his publications. (See Chapter XII)

Decorticate Preparations

At about the same era as that in which stimulation and ablation of the cortex was yielding information, radical extirpations of the "higher" centers were giving evidence of the functions of various other areas, and indirectly of the motor cortex.

Just as stimulation of cortex of rabbits, cats, dogs, primates, and any other rarer animal which happened to be available had shown that the more complex cortices of the "higher" animals possessed the ability for more discrete movement, so, radical removal of these cortices showed conversely that the sub-cortical motor function of the "higher" mammals

was far less adequate to cope with the exigencies of existence than that of lower forms (Smith, 1933; Ferguson and Fulton, 1932; Richter and Bartemeier, 1926).

From the experiments of Sherrington (1940), Magnus (1918, 1922, 1925, 1926) and Rademaker (1931), it became clear that decorticate and decerebrate dogs, cats, and monkeys each possessed distinct motor functions as did the intact animals.

The righting reflexes in particular were carefully examined by Magnus (1918), and the relation of the vestibular and proprioceptive apparatus to posture was described. It became clear that in the absence of the cerebral cortex a postural pattern is present which, both during rest and in movement, in all mammals, is extraordinarily like that of the intact animal, but which is simple and automatic in character, altering always in a stereotyped but often excessive way in response to given stimuli. The movements of the decorticate animal resemble those which are usually called associated movements in the intact animal. But in the latter, a tremendously complex "voluntary" pattern overlies and masks the simpler reflexes. For example, the movements of the decorticate monkey are so inappropriate and limited in character that they are entirely incompatible with life (Karplus and Kreidl, 1914; Bard, 1928). Although these animals can with adequate stimuli chew, swallow, vocalize, and right themselves, they can neither eat nor walk, all "voluntary" movements having been eliminated. It can be inferred therefrom that the motor function of the cortex is that of integrating and regulating the relatively simpler reflex movements in a highly complex manner into the "voluntary" purposeful movement of the intact animal. That practically all of the somatic motor functions of the cerebral cortex are subserved by areas 4 and 6 is indicated by the fact that bilateral removal of these areas produces a completely helpless animal, as limited in motor function as the decorticate "thalamic" preparation of Karplus and Kreidl (1914) (Bucy and Fulton, 1933; Bieber and Fulton, 1933, 1938; Fulton and Dow, 1938).

Anatomical Investigations

Although the histological studies of the motor cortex are dealt with elsewhere (Chapter II), it must be mentioned here that during the period when cytoarchitectural maps of the cortex were being evolved in detail, much of the histological material was being correlated with physiology. Thus, Sherrington first reported the study of Campbell (1905); the Vogts (1907, 1919) dealt largely with function in considering cytoarchitecture; Brodmann (1909) considered function; and such studies as those of Holmes and Page May (1909), on the origin of the pyramidal tracts, and

Mellus (1899, 1901, 1905), dealing with bilaterality of function, were instigated largely by functional considerations.

Earlier Reviews

Some earlier reviews of the literature on the above subjects may be found as follows: Monakow (1902, 1914), Rothmann (1907), Fulton and Keller (1932a), Fulton (1938), Foerster (1936b), Penfield and Boldrey (1937), and Wilson (1925). The selected writings of Hughlings Jackson were published in 1931 and 1932, those of Sherrington in 1940, Volume XIII (1934) of Research Publications of the *Association for Research in Nervous and Mental Disease*, was devoted to "Localization in the Cerebral Cortex."

PRESENT KNOWLEDGE OF SOMATIC FUNCTION OF THE CORTEX

During the past ten years much of the older material concerned with functional localization in the cortex has been adapted to more recent contributions along other lines so that today, although far from static, our concept of the cortical motor mechanisms is more definite than it has been in the past. There have been many previous publications which summarize special phases of this recent knowledge, such as the text on neurophysiology of Fulton (1938, 1943), the book by Penfield and Erickson (1941) concerned with epilepsy, and the many papers of Dusser de Barenne (1933a, 1935; Dusser de Barenne and McCulloch, 1938c), Hines (1929, 1937, 1940), Scarff (1940), and others.

Since this progress in investigation has come about largely through use of newer *methods*, they will here be described briefly; the *results* of the use of some of these methods will be cited in greater detail later.

Methods of Investigation

In recent years, refinements of the following techniques and procedures have facilitated observations on the motor functions of the cortex.

Anesthesia—More or less recent improvements in the use of local anesthesia have made possible the clinical observations of Cushing (1908, 1926), Foerster (1931, 1936b; Foerster and Penfield, 1930), and Penfield (1939; Penfield and Boldrey, 1937) which deal with localization of function in man. By present methods, conscious human subjects are now maintained in good general condition with normal blood pressure and are sufficiently responsive to testify accurately to their experiences during cortical stimulation and ablation.

Similarly, in animal experiments it has been shown (Fulton, Liddell, and Rioch, 1930; Fulton and Keller, 1932b; Keller and Fulton, 1931; Marshall, 1941) that certain of the barbiturates leave the cortex less excitable than others, and that the blood supply to the relatively excitable cortex under ether anesthesia is greater than under barbiturates (Laidlaw and Kennard 1940), but that under barbiturates when the cortex is less easily stimulated the hypothalamic blood vessels are relatively dilated These findings, together with long practice in the use of the drugs, now make possible the choice of anesthetic for the desired effect in a given operation or experiment. The procedure of Dusser de Barenne and his associates (Bailey, Dusser de Barenne, Garol, and McCulloch, 1940; Bailey, Garol, and McCulloch, 1941a, b), during which chimpanzees and monkeys have been kept under dial anesthesia with evenly excitable cortices for several days, is the peak of achievement in the use of such anesthetics

Surgery—Clinical neurosurgical techniques as first developed by Cushing (1908, 1926, 1928) have made possible an enormous number of procedures, so that today, in man, cortical stimulation and the effects of ablation can be studied uncomplicated by great changes caused by general systemic reaction to the operation. The process of recovery has been enormously accelerated also.

These techniques have been adapted to experimental purposes in many laboratories, most successfully for primates by Fulton (1934b, 1936b, 1937; Fulton and Keller, 1932a); Bard (1937-1938); Woolsey, Marshall, and Bard, 1942); Hines (Hines and Boynton, 1940); Barrera (Pacella, Barrera, and Kopeloff, 1942); and many others. Immediate observations as well as those on chronic preparations are now valid as never before

The special procedure whereby the Horsley-Clarke stereotaxic instrument is used for stimulation or destruction of deep structures has been of assistance in the study of motor activity and has been developed to a high degree in the laboratory of Ranson (Ranson, 1934; Harrison, 1938).

Cortical Destruction—In addition to the knowledge of function obtained from ablation and stimulation, there have been many attempts to destroy part or all of the motor cortex by other means The most successful of these have been: thermocoagulation (Dusser de Barenne, 1934a, b; Dusser de Barenne and Zimmerman, 1935), by means of which one or several layers of gray matter can be destroyed in a desired area without alteration in surrounding tissue; freezing (Trendelenburg, 1911; Hoff, 1929; Hoff and Kamin, 1930; Nims, Marshall, and Nielsen, 1941; Marshall, Nims, and Stone, 1941); and the use of various traumatizing chemicals such as alcohol, alum, blood serum, etc., which has culminated lately in the

production of chronic epilepsy in animals (Pacella, Barrera. and Kopeloff, 1942).

Chemical Methods—The use of the glass electrode whereby changes in pH may be recorded from the surface of tissue such as the brain (Nims. Marshall, and Burr. 1938) has made available an analysis of a phenomenon long known to have been present clinically, namely, the augmentation of cortical excitability and hence production of epilepsy by deep breathing (i.e. change in pH) The methods are well described by their various employers; the use of rebreathing in clinical cases by Rosett (1924) and in animals by Brody and Dusser de Barenne (1932); and use of the glass electrode by Marshall, McCulloch, and Nims (1939). Stone (1940a, b). Stone, Marshall, and Nims (1941), Gibbs. Gibbs, Lennox, and Nims (1942) and Nims, Gibbs, Lennox, Gibbs, and Williams (1940). The pH of the epileptic cortex has also been studied by Penfield (1933, 1937b); Penfield, Santha, and Cipriani, 1939).

Efforts to determine the chemical composition of the brain tissue itself, both in vivo and in vitro, have been used from early times and have been informative. Page (1937), in his book on the chemistry of the brain, has discussed the various methods of chemical analysis. They are divided by Page into the following groups study of substances in the blood bathing the brain; analysis of cerebral tissue at autopsy or operation; analysis of cerebrospinal fluid; analysis of the chemical consequences of activity; and study of tissue culture explants from the brain.

The study of drugs on the cortex is also an old and widely considered study. It has recently become of interest along several specific lines· the study of the effect of artificially produced convulsions on such psychopathic conditions as catatonia (Jasper and Erickson, 1941); the relation of vitamin deficiency to cortical function (Peters, 1937; Ochoa and Peters, 1938; Thompson and Johnson 1935), which is intimately concerned with the effect of cholinergic (Nachmansohn, 1940; Nachmansohn and Meyerhof, 1941; Williams, 1941) and of sympathomimetic drugs on motor status

In addition to the above studies of brain metabolism there have been investigations of the effects of disorders of the motor system on the general metabolism of the organism (Dusser de Barenne and Burger. 1924; Bruhn, 1934; Rakieten, 1935, 1936) concerned largely with spastic and flaccid states.

The use of strychnine by Dusser de Barenne (1924a, b) and his associates (Dusser de Barenne, Marshall, Nims, and Stone, 1941) has proved enormously valuable in functional cortical localization. Strychnine, which can be applied locally within the central nervous system, acts only on cell

bodies, exciting them to fire synchronously. The resultant disturbance as recorded by oscillograph, is a sudden spike-like voltage many times greater than the normal electric activity of the area strychninized It can be recorded from the axons and collaterals of any group of strychninized cells It is not transmitted unaltered to a second neuron. The axonal field of a group of cells, either on the cortex or elsewhere, can thus be disclosed.

Electrical Methods—Development of electrical methods, which has been dramatically illustrated to the world by the radio, has been almost as revolutionary in the physiological laboratories. Both stimulation and recording have been elaborated, and the study of individual neurons of synapses, and of complex cortical structures has contributed much to our knowledge.

There are now many adequate means of stimulation of the motor cortex which have supplanted the old, simple, and unreliable "Harvard" induction coil. The use of condensers has made available a more uniform type of stimulus (Wyss and Obrador, 1937); more recently, the thyratron (Penfield, 1939), the Sine wave (Hines, 1940), and the various developments from these, such as the stimulator "B" of Goodwin, described by Dusser de Barenne, Garol, and McCulloch (1941a) have all provided adequate stimuli in which the shape and frequency of the wave are accurately controllable.

An interesting but as yet not widely used method of study is that of Loucks (1934) and of Chaffee and Light (1934, 1935) in which electrodes, buried in a desired portion of cortex, are activated by bringing the intact animal within the influence of an electric field, thereby producing stimulation of the cortex adjacent to the electrodes. By this means, "remote" stimulation of the motor cortex may induce epilepsy in a relatively intact and normal preparation.

All recording of electrical activity from the cortex is now done by means of the oscillograph. This instrument may be used for analysis of action potentials of single axons as well as of all the more complex units of function of the central nervous system. Its adaption to the clinical electroencephalogram by Berger (1929) is now widely used (Gibbs and Gibbs, 1941).

Excitable Properties of Cortex in Relation to Somatic Motor Function

From the earliest times, it has been known that repeated stimulation of living tissue may not always produce the same result (Bubnoff and Heidenhain, 1881; Exner, 1882; Graham Brown and Sherrington, 1912). There

followed studies of nerve and muscle which produced chemical and physical definition of such terms as *"latency," "fatigue,"* and *"refractory period."* These subjects are still matters of great concern to medical students, for they are the basis of knowledge of the reactions of living cells. When analysis of cortical properties was begun it was at once obvious that the changes in excitability here were subject to the same variants, but that they were both too complex and too minute to be explained as simply. A number of other phenomena were then described, to be further analyzed with the development of more refined techniques. By far the greatest contribution has come from Sherrington and his pupils—Graham Brown, Leyton (Grünbaum), Eccles, Liddell, and Denny-Brown. Much of their work will be found in the volume of selected writings of Sherrington (1940).

Various names have been applied to the factors causing variation of response to cortical stimuli:

Facilitation of a response may occur with successive stimuli applied to one point. Under these circumstances (1) the response to a second stimulus of the same intensity as the first may be greater, i.e. there may be spread of response from one muscle group—say in a finger joint—to involve several muscle groups or fingers, or even the whole hand; or (2) a given point may, after an initial stimulation, respond to a stimulus which was at first sub-threshold. The characteristics of facilitation have been described in a series of articles by Graham Brown (1915a, b. c. d, 1916a. b), by Dusser de Barenne and McCulloch (1939a), and by Rosenblueth and Cannon (1942)

Extinction appears invariably when an appropriately timed second stimulus is applied to a given point. The expected second motor contraction may be either absent or diminished (Dusser de Barenne and Mc-Culloch, 1936a, 1939a; McCulloch and Dusser de Barenne, 1935, 1939), the response being subject to the state of refractoriness of the point stimulated.

Suppression, a third property, has been more recently described (Dusser de Barenne and McCulloch, 1939c, 1941a) and is less thoroughly understood than either facilitation or extinction. It is discussed in detail in Chapter VIII. Unlike facilitation and extinction, suppression is a property of certain cortical areas and is not universal to living neurons. Dusser de Barenne and McCulloch (1939c) discovered that in the monkey, cat, and chimpanzee, along the rostral border of area 4. there lies a strip of cortex (area 4s; figs. 91a, 97) which when stimulated will suppress electrical activity of the cortex, including that of area 4. Then motor activity cannot be produced by any form of stimulation therein. Further investigation revealed other suppressor areas rostral to area 6 (area 8) and in the

parietal region (figs. 91a, 97). Suppression of electrical activity has several unique characteristics, as yet not entirely explained, chief among which is the nature of its time relations which are unusually slow. Following stimulation of area 4s, as long as 10 minutes may elapse before suppression appears. Activity in the affected area 4 may then be suppressed for as long as 20 minutes. The relations of the various cortical suppressor areas are well described by Dusser de Barenne and McCulloch (1939e, 1941a, b).

After-discharge occurs following a strong stimulus applied to the cortex. That is, after the stimulus has been removed, there follows a series of discharges which gradually die out (Erickson, 1940) and which are "self-sustained" (Rosenblueth and Cannon, 1942). It is possible that this reverberation and reiteration, which in the motor system appears as a series of contractions of somatic musculature, is effected through the basal ganglia. It has been used in the measurement of the spread of cortical excitation (Erickson, 1940).

At the present state of knowledge, it can only be inferred that these infinitely complex properties of cortical excitability are, in the intact organism, the means whereby integration of the infinitely complex and variable coordination of voluntary motor activity is accomplished. It can further be assumed that injury to a part of this organization disturbs the various functional elements, thereby producing spasticity, tremor, paralysis or whatever is characteristic of a focal lesion affecting motor activity.

The details of the investigations of the electrical properties of the cortex may be studied further in articles by Lorente de Nó (1935a, b) and Lloyd (1941). (See Chapter III.)

There are several other factors directly influencing cortical excitability which will be mentioned here.

The effect of chemical changes on excitability is one of the most recent to undergo analysis. The most important methods for this are: the study of acetylcholine and cholinesterase during synaptic activity (Nachmansohn, 1940; Nachmansohn and Meyerhof, 1941); and the analysis of changes in pH with activity. This last has been carried out either by analysis of changes in chemical relationships of carotid and jugular blood during activity in man (Gibbs, Gibbs, Lennox, and Nims, 1942) or by direct measurement on the cortices of animals (Dusser de Barenne, McCulloch, and Nims, 1937; Marshall, McCulloch, and Nims, 1939; Stone, Marshall, and Nims, 1941). Since epilepsy represents a very large (if not maximal) discharge of cortical cells, it has been used extensively in this study of differences between resting and active cortex.

Alterations in acid-base relationships are accompanied by vasomotor changes. Penfield (1933) has been able to observe directly during opera-

tion that the pial blood vessels of man change appreciably in color and size after cortical stimulation produced by a focal epileptic attack.

There are many studies of the spread of excitability from one area to another and of the relationship of this spread to motor activity, usually to epilepsy, but these are discussed in detail in Chapter XIII.

Localization of Function

During recent years, functional methods of localization have done much to alter the maps of cortex originally differentiated by histological means, although there still remains a correlation between the two. One of the points to become clarified by these means has been that of the phylogenetic differences in structure and function. The constitution of the cortex of a rabbit (Brooks and Woolsey, 1940), cat (Langworthy, 1928), dog (Smith, 1935) and primate (Walker and Fulton, 1938) is well established, and the progress of encephalization of function can now be reasonably traced.

A profitable branch of this study has been that of various primate forms from the simpler tarsius and marmosets to the higher anthropoids (Fulton and Keller, 1932a; Fulton and Dusser de Barenne, 1933; Walker and Fulton, 1938). Penfield, through stimulation of many brains of humans and comparison of the resulting maps, has constructed detailed plans of the arrangement of stimulable motor points in man (fig 113 p. 348) (Penfield and Boldrey, 1937; Penfield and Erickson, 1941).

In 1932, Milch, removing small portions of cortex from pre- or postcentral gyrus of the monkey, subsequently traced the course of fibers from such regions to other cortical areas by means of Marchi degeneration, and thus demonstrated that within the sensorimotor field (areas 6, 4, 3, 1, 2, 5 and 7 of Brodmann; figs. 2a-2b, p. 11, and 95, p. 249) there were multiple connections having a definite order in number and distribution.

Dusser de Barenne (1933b), using the strychnine method, found that strychninization anywhere within this sensorimotor area would produce a pain response in a lightly anesthetized cat. Subsequent work in this same laboratory has shown more clearly the well-defined interconnections within the sensorimotor area of the monkey. The connections of this region with the remainder of the cortex are not extensive (Dusser de Barenne, Garol, and McCulloch, 1941b). There is some evidence of motor function throughout this region, as it is possible under certain particular conditions to produce peripheral motor responses by electrical stimulation of the postcentral gyrus (Dusser de Barenne, Garol, and McCulloch, 1941a). Furthermore, there are some gigantic pyramidal cells in both the postcentral gyrus and in area 6. Thus, although the characteristics of indi-

vidual parts of the sensorimotor sector are well differentiated, it has as a whole certain features which differentiate it from the remainder of the cortex.

By strychnine stimulation also, Dusser de Barenne and McCulloch (1936b) were able further to divide the sensorimotor cortex into leg, arm, and face bands (fig. 96). These experiments were carried out under dial anesthesia in the monkey. Later Rosenblueth and Cannon (1942) using the same species of monkey under chloralose, were unable to demonstrate these functional divisions, although by using dial they confirmed the findings of Dusser de Barenne and McCulloch.

The discovery of suppression (Dusser de Barenne and McCulloch, 1939c, 1941b) has made the most significant alteration in our concept of cortical interrelations (see Chapter VIII). The various "strip" areas of suppressor activity and their interrelations were described by Dusser de Barenne, Garol, and McCulloch (1941b) in the monkey; by Garol (1942) in the cat; by Bailey, Dusser de Barenne, Garol, and McCulloch (1940) and by Dusser de Barenne, Garol, and McCulloch (1941a) in the chimpanzee.

In the following discussion of the functions of the various parts of the somatic motor areas, reference is made to subdivisions as designated by the maps of Dusser de Barenne for both monkey (fig. 91a) and chimpanzee (fig. 97), and as shown in the frontispiece for man.

Area 4—In all primate forms area 4 lies just along the anterior lip of the central sulcus and is characterized grossly by the presence of numerous Betz cells in the fifth cortical layer. Its functions are almost entirely motor and its functional characteristic is the integration of discrete voluntary
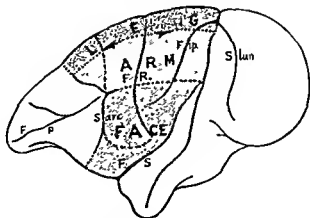
Fig 96—Sensorimotor cortex of *Macaca mulatta* as revealed by method of local strychninization. The dotted lines indicate boundaries between subdivisions of the sensorimotor zone, the shaded areas the extent of this zone. After Dusser de Barenne (1933a)

motor acts as described originally by Hughlings Jackson (1875) and later by Foerster (1936b).

Although the site of area 4 in man and monkey differs in detail, and although it is true that individual voluntary movements in man are more discrete than in monkey, the characteristics of area 4γ in man and of area 4 in subhuman primates are similar. By electrical stimulation in monkey and chimpanzee (Fulton, 1936b) and in man (Penfield and Boldrey, 1937), individual fine movements of finger joints, lips, tongue, or any distal portion of an extremity can be elicited. However, as stated by Penfield and Erickson (1941), these movements are never those accomplished normally by the cortex, but rather isolated components of the much more complex normal skilled and voluntary acts.

Representation of somatic musculature in area 4 is always of the same pattern (fig. 98) although actual convolutional relations vary with individuals. Distal portions of the extremities are always more widely represented than proximal, and hands are more widely represented than feet. The order of frequency of points producing movements in Penfield's humans was: hand (most frequent), tongue, lips, arm, face, thumb. Stimulation near the central sulcus or on its anterior lip always results in smaller
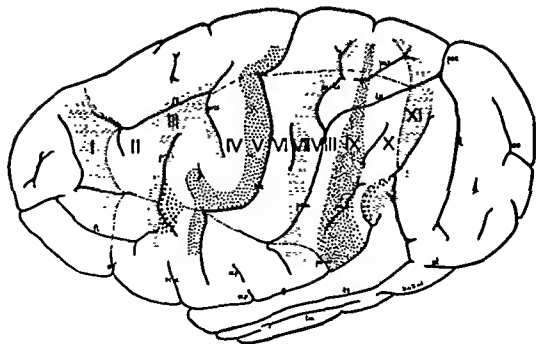
Fig 97 —The extent, location, and functional subdivisions of the arm area of the chimpanzee Areas I, III, VII, and XI are those from which suppression can be elicited After Dusser de Barenne, Garol, and McCulloch (1941a) (Cf fig 91b).

and more discrete movements than does stimulation farther rostral. In area 6 are integrated the largest and least differentiated responses.

Focal motor epilepsy in man has been found repeatedly to be related to small lesions affecting specific parts of area 4, and it is often the case that the first epileptic attack of a patient or the first movement of each successive attack is of one such small and particular muscle group It is usual that a *group* of muscles functionally associated are all affected as originally postulated by Jackson and that single muscles do not contract. During experimental cortical stimulation, however, we have frequently produced contraction of a single muscle, and there seems no reason why this should not be possible, although it is equally obvious that "voluntary" movement is seldom if ever so limited.

Although localization of motor function is more specific in area 4 than in other parts of the cortex, there is some functional overlapping within it, for it is known that large lesions of this area involving arm and leg cause greater and more permanent deficit *in the arm* than do lesions of the arm area alone (Kennard, 1936b). Also, following unilateral ablation of the leg area in a chimpanzee, removal of the contralateral leg area at a second
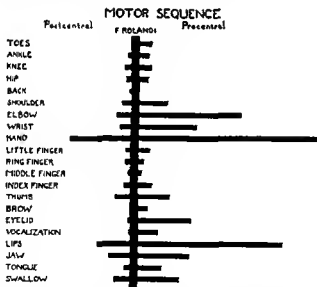
Fig 98—Chart of motor sequence for right hemisphere, indicating the sequence of motor responses in the Rolandic cortex from the median fissure (toes) to the Sylvian fissure (swallow) The broad vertical line represents the fissure of Rolando The length of individual horizontal lines to right indicates the proportional number of points anterior to the central sulcus Their length to the left indicates the number of points posterior to that fissure which gave responses in the part as shown by the names in the column at the left All face movements are included under the heading "lips" Hand movements include movements of all fingers together After Penfield and Boldrey (1937)

operation caused increased deficit of the leg affected by the first operation (Fulton and Sheehan, 1935)

The paralysis or paresis produced by destruction of part or all of area 4 in all primate forms is as characteristic of that area as is its epilepsy. Extirpation is followed immediately by a complete and flaccid paralysis which is, however, only transient in the monkey and chimpanzee and which shows some recovery in man. Recovery begins in the proximal joints and appears last in hands and fingers. The ability to move is gradually regained, particularly gross movements. Reflexes become hyperactive, but increased resistance to passive manipulation does not appear unless areas 6 and 4s are injured also. After complete destruction of the representation of a limb or part in area 4, discrete voluntary movements never reappear, although postural and associated movements may be adequate for walking and other postural adjustments. Isolated discrete movements such as prehension are never possible.

The relation of area 4 to the pyramidal tract has been discussed elsewhere (Chapter VI). It should be remembered at this point, however, that most, but not all, of the direct cortico-spinal tract degenerates when all of area 4 is removed; that large pyramidal cells are found in areas 4s and 6 and in the postcentral gyrus, but that most are in area 4 (see Chapter II). Hence, area 4 the true motor area, must be associated with mediation of impulses chiefly via the pyramidal or direct cortico-spinal tract.

Placing and Hopping Reactions. The presence or absence of normal function within the motor area can be tested by means of the placing and hopping reactions in animals and to some extent in man, as described by Bard (1937-1938). If the arm or leg of an animal is brought in contact with an object, such as the side of a table, the limb will at once be raised and placed upon the table. Similarly, if an animal is held over a flat surface with one limb in contact with this surface and moved in either direction, it will "hop" with that leg, keeping it in place beneath the body. The afferent side of the reflex arc may be either proprioceptive or tactile in the case of placing but is only proprioceptive in hopping. Neither reflex will occur if parietal cortex is destroyed on both sides, but when the afferent part of the reflex arc is intact, injury to area 4 will affect these responses (Brooks and Peck, 1940). This is perhaps the simplest reflex performance which has been found dependent on area 4, and hence is useful in evaluation of its function. It can be used in children, but not in adults. It is absent in infants of all species tested but appears, possibly, at the time of beginning function of the pyramidal tract.

Area 4s—In 1936 Hines reported that the anterior border of area 4 in the macaque had specific physiological characteristics which differentiated

Fig 99—Map of excitable areas of human cortex, adapted from the Vogts. After Foerster (1936b)

it both from area 6 anteriorly, and from area 4 lying on the other side. Ablation of this region, either unilaterally or bilaterally, resulted in transient spastic paralysis. Removal of tissue in area 6 rostral to this strip resulted in forced grasping but not in spasticity. Hines, therefore, separated the cortical region responsible for spasticity from the larger motor areas, lesions of which cause syndromes which include spasticity. Although this finding has not been verified by isolated ablation in man, it is to be expected that it exists, for reflex grasping and spasticity are very commonly found separately.

McCulloch, Graf, and Magoun (1946) have demonstrated that efferent fibers from area 4s in the monkey diverge from the cortico-spinal tract in the pons to end in the reticular formation of the tegmentum of the bulb. These are presumably the fibers having to do with the relaxation of peripheral muscular contraction (Ward, 1947). The experimental observations of Wagley (1945) that interruption of pathways in the ventral division of the lateral columns or in the ventral columns of the spinal cord, without injury to the pyramidal tracts, is followed by some of the phenomena of release, may indicate that the secondary inhibitory efferent fibers descending to the spinal cord from the bulbar reticular formation may pass downward in this part of the spinal cord. Some unpublished observations of Lettvin support this assumption and further indicate that these inhibitory fibers may terminate upon internuncial neurons in the anterior grey horn which then transmit the inhibition to the anterior horn cells.

Dusser de Barenne and McCulloch (1939c) found that this same strip of tissue, now called area 4s (figs. 91a, 97), possessed the quality of "suppression" described above. Further investigations by the same authors and by Garol (1942) have identified this strip in the cat, monkey, and chimpanzee and have found it to be part of a series of strips all acting as suppressors which bound the other regions of the sensorimotor cortex. Strychninization has established direct functional connections from area 4s to caudate nucleus (Dusser de Barenne and McCulloch, 1938c) These have not, however, been seen by Marchi degeneration following lesions made in area 4s (Verhaart and Kennard, 1940). It is possible that this is due to the absence of myelin in such connections, since Ramon y Cajal (1909-1911) described collateral fibers entering the basal ganglia from the adjacent part of the internal capsule.

Bucy and Garol (1944) have demonstrated the existence of area 4s in man by means of electrical stimulation.

Although the details of these suppressor areas remain to be worked out, the characteristics of suppression, which are so different from those of any other excitable characteristic of the central nervous system, together with the implications which a suppressor area has for "higher" integration of
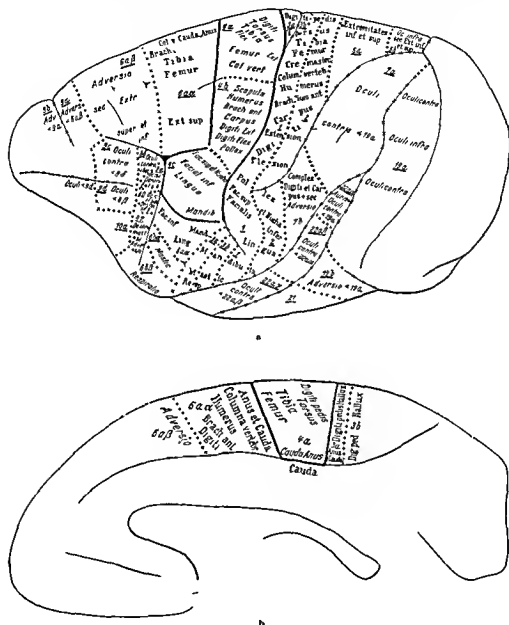
Fig 100—Cytoarchitectural and functional subdivisions of the cerebral cortex in the monkey (cercopithecus). After C. & O. Vogt (1919)

function, makes the discovery of these areas one of the most interesting of recent findings concerned with the cerebral cortex.

Area 6—The region lying rostral to area 4s, which is still a portion of the sensorimotor areas, has specific histological characteristics described elsewhere (Chapter II). From its cell structure it has been divided into areas 6 and 44. The subcortical connections of areas 6 and 44 are "extra-pyramidal" except for a few direct cortico-spinal fibers. Confusion as to their structural boundaries exists because there have been differences of opinion as to the limits of area 8. For purposes of functional differentiation, the anatomical divisions of Richter and Hines (1938; fig. 101) for the monkey and of von Economo and Koskinas (1925; fig. 3a) for man are more useful than others since they describe area 8 (area FC of von Economo; fig 3a) as extending to the mid-line (see also frontispiece). In the discussion to follow, that region rostral to area 6 which integrates eye movements will be considered as area 8, although, as will be shown later, this is not entirely satisfactory. (See Chapter XII.)

Area 6 lies between areas 4 and 8 (fig. 101 and frontispiece) and is therefore bounded on both sides by a suppressor area—8 and 4s (figs. 91a, 97). It is a motor area within which there is some localization of function, but nothing as discrete as that within area 4. The effects of stimulation of area 6 have been well described by Fulton (1937) and Wyss and Obrador (1937). Bucy (1933, 1936) summarized them as follows:

1 Stimulation of area 6 of the primate brain gives rise to (a) Sustained contractions of moderately small groups of muscles in the contralateral extremities These responses are mediated by fibers which pass to area 4 (b) Complex progressive and rhythmic movements in the contralateral extremities, which are effected at least in part by fibers which are direct projection of area 6 independent of area 4 (c) Responses in the ipsilateral extremities, principally the lower ones, and the tail (d) Torsion movements of the trunk and pelvis

2 The threshold of area 6 is higher than that of area 4, becoming increasingly greater for each of the four types of response in the order b-c-d, except for c and d which are essentially the same
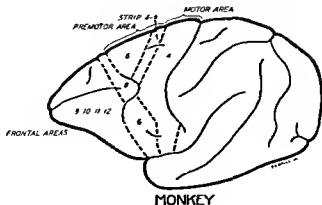
Fig 101—Map of cerebral cortex of *Macaca mulatta*, showing area 8 extending to mid-line After Richter and Hines (1938)

3 The responses of area 6 are much more susceptible to anesthetic drugs, especially the barbiturates, than the responses of area 4

4 The movements elicited from area 6 are much more prone to pass into epileptiform after-discharge than are those evoked from area 4

The syndrome which results from lesions in area 6 is well known. There is marked bilaterality of function, much more pronounced than in area 4 (Fulton, 1933-1934, 1934a, 1937; Kennard, Viets, and Fulton, 1934; Richter and Hines, 1934). Reflex grasping or forced grasping (Fulton, 1934a; Fulton and Dow, 1938) is the most unmistakable sign of disturbance of function within area 6, probably in its rostral portion only. Its existence in the newborn (Allen, 1939; Bieber, 1940; Bieber and Fulton, 1933; Halverson, 1937; Richter, 1931), its disappearance with the acquisition of voluntary motor activity, and its re-appearance in pathological instances have incited many discussions (Wilson and Walshe, 1914; Fulton, 1934a).

As stated above (in the discussion of area 4s), forced grasping may occur with or without spasticity. The latter is most often true in man where a reflex involuntary grasp may be found without any other change in reflex status, tonus, or motor performance. It may occur in the chimpanzee and monkey as well. The greater differentiation of signs in man may be due to the fact that, with elaboration of the frontal cortex, area 6 becomes both larger and more highly differentiated than in the lower primates

Reflex grasping, especially when the lesions are bilateral, is commonly associated with other changes in the more complex phases of motor performance. Particularly in man, phenomena such as apraxia and perseveration appear. Hypomotility together with indifference or apathy are often observed in such patients, and similar traits are found in monkeys (Bianchi, 1922).

Spasticity, with or without reflex grasp, is usually present following lesions of area 6, although it is more marked if the lesion includes area 4s also. It is greatest and most long-lasting in the monkey and chimpanzee when all of areas 4, 4s, and 6 have been removed.

By spasticity is here meant simply an increased resistance to passive movement together with increased tendon jerks. The resistance is of the "clasp-knife" variety, i.e., it is greatest during the intermediate part of a passive flexion or extension, but becomes less when the limb reaches either extreme of its movement. This is the type of increased resistance which has been thought to be due to heightened lengthening and shortening reactions.

Area 44—Of area 44 (frontispiece and figs. 8, 9, 17) there is little known as yet which differentiates it from the closely adjacent areas integrating

simpler motor functions of the eyes (area 8) and of the face, such as tongue, lips, and pharynx (Walker and Green, 1938; Dusser de Barenne, McCulloch, and Ogawa, 1938), which are dependent on the face divisions of areas 4, 4s, and 6. Its functions are related to movement of these parts in all primate forms.

In man, area 44 has been elaborated into the speech area of Broca, whose functions have been analyzed largely through the study of motor aphasia, a subject at once too large and too specialized to consider further here (Nielsen, 1936).

Area 8—Although this paper deals largely with areas 4 and 6, no discussion of cortical somatic motor function should exclude area 8, because it has somatic motor functions which are often closely associated with those of the adjacent area 6. Moreover, since the border between areas 6 and 8 (fig. 101) is not sharply defined, either anatomically (Walker, 1940a) or functionally, it must be considered as part of the motor areas and as having functional characteristics very similar to those of area 6, except that, in the case of area 8, the movements elicited have to do primarily with the extrinsic muscles of the eye. The excitability characteristics of areas 6 and 8 also are very similar. Each has a high threshold and requires a long stimulus by a relatively slow wave compared with that which will excite area 4 (see Chapter XII).

Mesially in area 8, i.e., rostral to area 6, lies an area stimulation of which produces pupillary changes, lid movement, and conjugate movement of the eyes. Often this is accompanied by head movement which merges with tonic movements of head and neck, such as are commonly elicited from area 6 just caudal to 8. Farther laterally, within the arcuate sulcus in the monkey, the primary movement on stimulation is usually conjugate deviation of the eyes, followed by head, *away* from the side of the stimulus. *Ablation* of this area causes transient conjugate deviation of the eyes *toward* the side of the lesion and a circling of the animal in the same direction (Kennard and Ectors, 1938). More laterally still, stimulation produces eye and head movements at points very close to those which will evoke primary discrete movement of other parts of face or neck musculature, in face areas 6 and 4 (Smith, 1936) (see Chapter XII).

Relation of Postcentral to Precentral Areas

The remainder of the sensorimotor cortex, the parietal region, is closely associated with the precentral areas in several ways. Anatomically there are known to be heavy U-fibers connecting the two, and direct corticospinal efferents descend from the parietal regions (Levin and Bradford,

1938) (see Chapters IV, V, VI). Strychninization has shown that there are direct functional connections (Dusser de Barenne, Garol, and McCulloch, 1941b) (see also Chapter VIII and fig. 103). The exact motor function of the postcentral area is in doubt, but it is probably minimal in both man and monkey, for its removal affects motor performance only indirectly by alterations in sensory perception (Kennard and Kessler, 1940).

There are two other signs related to disturbances of motor function which have been associated with the postcentral region, namely flaccidity and atrophy.

Flaccidity, or diminished resistance to passive manipulation, probably occurs transitorily in any cortical paralysis, but with recovery of function it is swiftly converted to spasticity following lesions involving area 4s, and disappears with the paresis following lesions of area 6. Ablations restricted to area 4 cause more enduring flaccidity and paresis, especially in man, but in the monkey, when 4s is presumably not injured, the resistance to passive manipulation returns during recovery to about normal, and tendon reflexes become slightly hyperactive. The degree of recovery of the flaccidity is about the same as that of paresis in individual instances.

Pure parietal ablations produce a much longer-lasting flaccidity in the absence of true motor paresis. Such monkeys show loose and flail-like resting limbs, which may, however, be voluntarily moved both quickly and accurately. With recovery they may have definitely increased tendon reflexes at a time when resistance to passive manipulation is markedly less
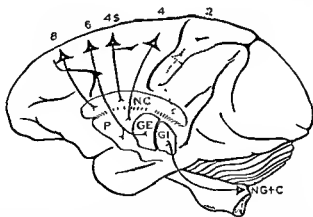
Fig. 102—Cortico-striatal connections in *Macaca mulatta*. *NC*, nucleus caudatus; *P*, putamen; *GE*, globus pallidus externus; *GI*, globus pallidus internus. Modified after Dusser de Barenne, Garol, and McCulloch (1941b). (Cf. fig. 84)

in the affected limb as compared to that in the normal side. This same finding of increased tendon reflexes and flaccidity may appear also, but for a much shorter period, during recovery from lesions restricted to area 4. It is difficult to explain on the basis of heightened stretch reflexes which are ordinarily thought to be the cause of spasticity.

These data indicate that in monkeys and chimpanzees lesions of caudal parts of the sensorimotor cortex tend to produce flaccidity, whereas those in the region of area 4s make greatest spasticity. In man, flaccid cortical paralyses are rare, although they do occur, and it is a common clinical belief that cortical lesions, if caudal, are apt to produce flaccid paralysis, but if situated rostrally, the paralysis is spastic.

Atrophy, like flaccidity, may appear with paresis of cortical origin (Guthrie, 1917-1918). It is apt to be more marked in flaccid than in spastic extremities. (See Chapter XIV.)

I	II	III	IV	V	VI	VII	VIII	IX	X	XI
Y▲	—	—	—	—	—	—		—		
Y	Y▲	Y	Y	Y	Y	•			Y	
—	—	Y▲						—		
		Y	Y▲							
			Y	Y▲	Y					
		Y	Y	Y	Y▲					
					Y	Y▲				
					Y	?Y	Y▲			
			Y		Y		?Y	Y▲		
					Y			?Y	Y▲	Y
—	—	—	—	—	—	—		—		▲Y

ANTERIOR BORDER   F'CE   POSTERIOR BORDER

Fig 103.—Table of direct functional relations between the various cortical bands of the arm subdivision of the chimpanzee. Anterior and posterior borders are the limits of sensorimotor cortex. The suppression of electrical activity of various bands on strychninization of bands I, III, VII, and XI is indicated thus —, *FCE*, fissure centralis, •, no certain evidence, Y, "firing" (see fig 97). After Bailey, Dusser de Barenne, Garol, and McCulloch (1940) (Cf fig 91b, p 233)

Effect of Other Structures on Function of Precentral Motor Cortex

Thalamus—The present concept of the thalamus is that of an organizing way-station connecting afferent impulses with the cerebral cortex, chiefly in the parietal region. Since it is concerned largely with sensation little could be discovered of its function by use of experimental animals beyond that inferred from anatomical studies (Walker, 1938a) until the development of three recent techniques: (1) strychninization; (2) measurement of the cortical potentials which result from peripheral stimulation; (3) the use of the conditioned reflexes.

Strychninization of the precentral cortex of a lightly anesthetized cat (Dusser de Barenne, 1937b; Dusser de Barenne and Sager, 1937; Dusser de Barenne and McCulloch, 1041a) causes signs of sensory irritation. Strychnine placed at various points throughout the circuit has demonstrated in addition, by oscillographic recordings, an orderly connection of the various thalamic nuclei with the motor areas, not only indirectly via parietal lobe but directly also (McCulloch and Dusser de Barenne, 1940). As will be shown in the next section, parts of these circuits pass through the striate nuclei. Direct connections from the thalamus to area 4, as well as to the postcentral gyrus, have been determined by the same method.

A series of papers by Derbyshire, Rempel, Forbes, and Lambert (1936), Forbes and Morison (1039), and Dempsey, Morison, and Morison (1940-1041) have traced the course of afferent impulses from stimulated peripheral nerves to cortex. The findings are summarized in the last paper (1040-1941). A primary response to stimulation of a sciatic nerve of a cat appears as activity in the leg portion of the sensorimotor cortex with a latency of 8-10 Msec. This response is abolished by lesions which destroy the thalamus or the lateral division of the medial lemmiscus, but not by lesions elsewhere. It is inferred by the authors that this pathway has to do with sensations of touch and proprioception.

Basal Ganglia—Knowledge of the functions of the basal ganglia in relation to the motor cortex is at present at a stage of active development, and many of the old uncertainties have recently been eliminated.

As the structure of the large cells in the basal ganglia is of a motor type, and as destruction within these nuclei has long been considered clinically to produce disturbances in the rhythm of movement, such as tremor or athetosis, it was early decided that the motor cortex must be related to these relatively large structures. In vertebrates, such as birds, with very little cortex, the function of the basal ganglia is unquestioned, but in higher animals repeated attempts to investigate the function of caudate

nucleus, putamen, and globus pallidus had brought forth nothing of positive nature (Rioch, 1940) Early effort at stimulation and ablation (Wilson, 1925) of these nuclei produced no alteration in motor status However, very early in the history of surgery of the motor cortex (see Bucy, 1940) it was found that partial ablation of the precentral motor cortex in man subdued the involuntary movements which resulted from disorders of basal ganglia As will be discussed in Chapter XV, much theory and practice has been applied during the last few years to this matter in an effort to relieve the distressing symptoms of involuntary motor acts in man (Bucy, 1940, Meyers, 1940, 1942a, b).

The experiments of Mettler, Ades, Lipman, and Culler (1939; see also Mettler, 1940) were the first to furnish a lead as to function of the basal ganglia by use of experimental animals They reported that stimulation of the caudate and putamen *during repetitive stimulation of the motor cortex* would markedly alter the type of response elicited Interdependence of function of the two regions was thus clearly shown. In this laboratory (Kennard and Fulton, 1940, 1941), confirmation of this has been complete Tremor, athetoid movements and spasticity have been produced by ablation of portions of caudate and putamen *together with* area 6 of the cerebral cortex in both monkeys and chimpanzees Isolated ablations from basal ganglia do not alter motor performance unless they are very large and unless they are bilateral. Much smaller lesions of basal ganglia are effective if area 6 is removed also. Bilaterality of function and lack of localization within the nuclei probably account for the negative results obtained from lesions made by previous investigators It is now certain that by interaction with the precentral motor cortex, area 6 in particular. the basal ganglia function to coordinate and "smooth" voluntary motor performance, as integrated through the motor cortex It is not yet certain by what anatomical means this is brought about. for, although Dusser de Barenne and McCulloch (1938c) and Dusser de Barenne, Garol, and McCulloch (1940) found functional connections from cortex to basal ganglia by strychninization, the direct anatomical connections which have thus far been demonstrated are slight and probably non-medullated (Verhaart and Kennard, 1940). It is of interest that Dusser de Barenne and McCulloch report functional localization within the system which is not related to distribution of limb movement but which connects the suppressor area 4s to the caudate nucleus, and area 6 to the putamen (fig. 102, p. 270).

Cerebellum—The interrelations of cerebrum and cerebellum with respect to motor performance have been recognized clinically for many years, largely because occasionally a tremor which results from frontal lobe disorders has been diagnosed as due to cerebellar disease in man (Gordon,

1934) (see Chapter X). There is as yet no satisfactory explanation of this on an experimental basis, since the majority of lesions of the frontal cortex do not produce tremor. It is possible from recent evidence (Kennard and Fulton, 1940) that it is due to involvement of basal ganglia. The effect of cerebral cortical lesions on tremor of cerebellar origin has been shown by Fulton (1931, 1936b); Fulton, Liddell, and Rioch, 1932) (see Chapter XV) In a hemidecerebellate monkey removal of the opposite cerebral hemisphere abolishes the tremor, removal of area 4 transiently diminishes it, but, in contrast, removal of area 6 is followed by its augmentation Thus a marked interdependence of these two motor areas of the central nervous system has been shown.

Discussion of Functional Organization of Cortical Motor Activity

In this review, since it has been impossible to quote the very large bulk of material in detail, an attempt has been made to cite representative authors and the methods they have used in developing our present concept of the motor functions of the cortex. It is evident that the first discoveries were those of discrete focal cortical areas responsible for individual movement, but later study of the interrelations of these focal areas with other cortical and subcortical units has produced the concept of a functional whole which is more in harmony with the execution of coordinate voluntary motor activity It now seems certain that the cortical meshwork postulated by Hughlings Jackson has been traced in many of its details, so that the connections of motor areas to pre- and postcentral cortex and to subcortical centers can be visualized.

During these studies some evidence has appeared which points to another type of functional interrelationship, namely, a capacity within this system for variation or for reorganization of function under certain circumstances. The studies have been made largely on recovery of function following lesions of the central nervous system. Observations on infants and young animals have been particularly valuable

Motivation has been found to affect recovery after injury of cortical tissue in rats by Lashley (1938) and in monkeys by Biedl (1897) and by Ogden and Franz (1917-1918). Ogden and Franz produced paresis in monkeys by unilateral cortical lesions and reported marked increase in rate of recovery of the affected limb if the sound ipsilateral limb was bound up and immobilized so that the paretic one must be put into use.

The relation of use to stimulation by cholinergic drugs is under investigation at present, for it has been found that both peripheral nerve lesions

(Wolf, 1940) and cortical ablations (Ward and Kennard, 1942) are recovered from more rapidly when cholinergic drugs are administered to the subject. Most of the practice of physiotherapy today is, of course, based upon recovery of function with use. It is possible that cholinergic substances play a role in such recovery.

Recovery of function may be based also on *cortical organization within the normal hemispheres*. Thus, although leg and arm area 4 are physiologically separate entities, removal of both produces greater deficit in a limb than does removal of the center for that limb alone (Kennard, 1936b). Representation in both hemispheres also may be responsible for the recovery of function which follows removal of the area *most* responsible for a given movement (Fulton and Sheehan, 1935).

Age markedly affects recovery, for cortical ablations from infant monkeys during the first weeks of life, and from older animals of the same species during all stages of subsequent development, have shown that the cerebral cortex of the young possesses a greater capacity for reorganization of motor activity following partial ablations of the motor areas than does that of the adult (Kennard, 1936b, 1938, 1940, 1942). Thus, bilateral ablation of areas 4 and 6 from an adult monkey is followed by no or, at best, little recovery of voluntary function (see also Chapter XIV, p 384). Such an animal remains unable to stand or feed but shows the simple reflex righting patterns (Bucy and Fulton, 1933; Bieber and Fulton, 1933, 1938). In contrast, after removal of similar areas, a young infant monkey shows very little change in motor status from its preoperative level Moreover, young animals under about six months recover sufficiently after loss of areas 4 and 6 bilaterally to be able to care for themselves adequately; those operated on during the first weeks of life show more adequate motor performance than the older infants During the remainder of the first two years of life (this species, *Macaca mulatta*, matures at four years of age) these monkeys still retain some of the capacity to reorganize the integration of motor performance.

That the remaining cortex is responsible for this integration has been shown by subsequent removal of non-motor areas, such as frontal poles or postcentral regions. In the normal animals this alters motor status little if at all, but when extirpated after the previous removal of areas 4 and 6 in infancy, the ablation of these areas markedly affects the capacity for organized voluntary movement.

It is probable that such capacity for reorganization of function exists in the human infant also (Kennard, 1940a) since relatively large injuries received at, or before, birth very often cause little or no deficit when compared to that produced by the equivalent lesion in an adult.

In a discussion of the factors underlying this capacity for recovery Jacobsen, Taylor, and Haselrud (1936) offer three possibilities (1) the subject learns to adjust to the loss of function; (2) there is vicarious assumption of function by some other part of the nervous system not previously concerned with this function; (3) there is reorganization within a partially destroyed system. Present evidence indicates that in the case of paresis it is impossible to adjust to the loss of function, and there is no need for the second assumption if one considers the entire cortex (except the occipital and temporal lobes) to be one functional unit. We must, therefore, conclude that when motor performance is reintegrated after ablation of areas 4 and 6, there has been only a partial destruction of the central representation of the motor system.

Physiological studies of hemiplegias in both man and monkey show that the marked capacity for functional restitution exists throughout the interval before development of adult motor activity occurs. Since very recent anatomical studies of the cortex of the young human (Conel, 1939, 1941) show that the gray matter of the one-month-old child has neither the cellular nor dendritic structure of the adult, it is entirely possible that part of the reorganization may be due to completion of an anatomical organization which had not entirely matured at the time of injury. If during this early period dendritic synaptic connections are not fully formed, it is conceivable that during posttraumatic development unusual connections are formed which would not normally have functioned. Such a concept of the organization of the motor functions of the cortex is possible, if the normal cortex is visualized as an infinitely complex network of interrelated neurons, constantly responding to chemical and electrical fluctuations, capable under normal circumstances of adjusting to disturbances of cortical and subcortical structure within limits which become more restricted as the age of the organism increases.

Chapter X

RELATIONSHIP TO THE CEREBELLUM

Percival Bailey, M.D., Ph.D.

Professor of Neurology and Neurological Surgery
University of Illinois College of Medicine
Chicago

OUTLINE OF CHAPTER X

Relationship to the Cerebellum

RELATIONSHIP TO THE CEREBELLUM

IT HAS LONG BEEN KNOWN that, in phylogenetic development, the cerebellar hemispheres develop simultaneously with the cerebral hemispheres. In such an aberrant offshoot as the birds the almost complete absence of the cerebral cortex (Bremer, Dow, and Moruzzi, 1939) is accompanied by absence of cerebellar hemispheres and pontine nuclei (Ariëns Kappers, Huber, and Crosby, 1936). Moreover, if the cerebral hemisphere is injured early in the development of the human being there results a lack of development of the contralateral cerebellar hemisphere (Turner, 1856). Facts such as these indicate that there is some essential relationship between the cerebral hemisphere and the opposite cerebellar hemisphere. As evidence accumulates it becomes apparent that areas 4 and 6 are particularly implicated. We propose to summarize here the pertinent data and attempt to formulate the meaning of this relationship.

Anatomical connections are sufficiently complex in the central nervous system to make it obvious that no part of it performs any function independent of, and isolated from, many other parts. Functions are not localized in specific parts of the system, but all are parts of a functioning whole. Nevertheless, experience has proved that destructive lesions cause varied symptoms, depending on the localization of the injury, and that a given function may be deranged by injuries at different places in the nervous system, making it necessary to distinguish anatomical complexes utilized by certain functions. Even before the functional significance of an anatomical complex is known its study may indicate what functions it may serve. The great efferent pathway from areas 4 and 6 is the effector pathway of many functional complexes, but the anatomical connections between the motor area of the cerebral cortex and the cerebellar hemisphere are sufficiently prominent to indicate that the latter exercises an important influence on its functioning.

All of the subsequent discussion refers to the macaque monkey unless otherwise noted. This is the only primate on which much experimental work has been done. Whether the findings are valid for man is often conjectural, but what scanty and imperfect data we have indicate, in spite of a continued evolution, a broad general correspondence.

Experimental Anatomical Data

Corticopontine Projection—The exact origin of the corticopontine fibers is still not definitely settled. Most authors agree that no such fibers arise from the frontal cortex anterior to area 6, although Mettler (1936)

believes that some come from area 9, and Levin (1936) believes that some may arise from the inferior frontal gyrus. Corticopontine projections from areas 4, 4s, and 6 have been described by Levin (1936), by Sunderland (1940), and by Verhaart and Kennard (1940), all using the Marchi method. In addition, temporopontine fibers have been found by Mettler (1935-1936) and by Sunderland (1940), but not by Rundles and Papez (1938) or by Bucy and Kluver (1940). Parietal pontine projections have been described by Mettler (1935), by Rundles and Papez (1938), by Sunderland (1940), and by Clark and Boggon (1935). There seems to be general agreement about the parietal projection and also concerning the less numerous occipitopontine fibers (Mettler, 1935a; Sunderland, 1940).

The differences in the findings of various authors may be due to the uncertainties of the Marchi method, especially concerning the termination of these systems. Sunderland (1940) found that all of the frontopontine fibers pass through the posterior limb of the internal capsule and the medial third of the peduncle. They appear to end ipsilaterally in approximately the rostral three-fourths of the pons, about the dorsal part of the pontine nuclei.

Pontocerebellar Projection—All investigators are in accord that the pontine nuclei send their fibers to the cerebellar cortex through the middle peduncle, mainly to the contralateral hemisphere, but also some to the vermis and perhaps a few to the homolateral hemisphere. Marchi studies have been made mainly on lower vertebrates (Besta, 1913; Dow, 1935), but Spitzer and Karplus (1907) made two crude experimental lesions in the pons of macaques and found degeneration, after crossing, in the posterior part of the anterior lobe and in the anterior part of the posterior lobe.

Sunderland (1940) found diffuse retrograde degeneration in the contralateral pontine nuclei following destruction of the lobulus simplex, lobulus ansiformis, and lobulus paramedianus but not from a lesion in the lateral part of the culmen. He made no lesions of the paraflocculus or flocculonodular lobe. One lesion of the anterior lobe caused no retrograde changes in the pons.

Recent studies by Brodal (1940) on rabbits with a modified Gudden technic indicate that more localized projections may be found.

Cerebellum—After many attempts to subdivide the cerebellar cortex in such a manner as to have the anatomical subdivisions reflect functional differentiation it is becoming evident that the most fruitful scheme for both laboratory and clinic (Bailey, 1942) is that first suggested by Ingvar (1928) into archicerebellar (flocculonodular), paleocerebellar (spinocerebellar), and neocerebellar lobes (fig. 104a). In birds neocerebellum, cerebral
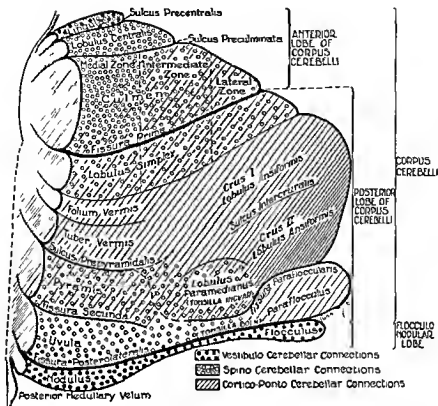
Fig 104a—Scheme of the cerebellar cortex Divisions are indicated after the terminology of Larsell (Reproduced with the permission of Dr Robert S Dow)

cortex, and pons are all practically absent (Ariëns Kappers, Huber, and Crosby, 1936). In mammals all three develop simultaneously and reach their climax in man. It is not supposed that the neocerebellar portion is simply added by juxtaposition to the older parts but, as Winkler (1923) pointed out, it rather grows by intussusception as well as apposition. It includes not only the cerebellar hemispheres (lobulus ansiformis, lobulus paramedianus, paraflocculus) but parts of the vermis also (folium et tuber vermis) and parts of other lobules. It is within these parts that the ponto-cerebellar fibers terminate.

Cortico-Nuclear Projection of the Cerebellum—There is very little information concerning this projection in primates. Clarke and Horsley (1905) made cortical lesions in four macaques and followed the degeneration by the Marchi method. In Rhesus 6 the culmen was undermined. No degeneration was found in the dentate nucleus but there were numerous degenerated fibers in the dorsal surface of the globose and much heavier degeneration in the fastigial and tectal nuclei. In Rhesus 12 the uvula

and pyramid were undermined. No degeneration was found in the globose or dentate nucleus but there were many fine degenerated fibers in the dorsum of the fastigial and tectal nuclei. In Rhesus 22 the uvula and pyramid were again undermined. There was no degeneration in the dentate nucleus but numerous degenerated fibers in the fastigial nucleus. There were degenerated fibers also in the globose nucleus but it had been injured directly. In Rhesus 23 eight folia of the lobulus quadrangularis were undermined and the neighboring lateral part of culmen injured. There were some fine degenerated fibers in the inner aspect of the posterior pole of the dentate nucleus and numerous fine fibers in the globose, fastigial, and tectal nuclei.

These few experiments indicate that there is a topical projection on the cerebellar nuclei. The probability is increased by the results in cats, rats, and rabbits where a definite projectional distribution has been proven (Jansen and Brodal, 1940; Dow, 1935). Their experiments indicate that the most lateral parts of the cerebellar hemispheres—the lobulus ansiformis and paraflocculus—project in the dentate nucleus of the same side, while the more medial parts of the lobulus ansiformis and the lobulus paramedianus send fibers to the homolateral intermediate nucleus. These are the most definitely neocerebellar parts of the cerebellar cortex; with the remaining cortex we need not here concern ourselves.

The exact homology of the intermediate nucleus in man is disputed It is accepted that the human dentate nucleus is composed of an older dorsomedial part and a newer larger ventrolateral part (Brouwer, 1920). It is not certain whether the human paleodentate is homologous with the nucleus interpositus or with the dentate nucleus of lower forms; the matter is not of much importance for our present purpose since all parts of the dentate nucleus send their fibers out through the brachium conjunctivum

Projection of the Cerebellar Nuclei—Mussen (1927) made lesions in the nuclei with the Horsley-Clarke stereotaxic machine and found, after lesions of the dentate and emboliform nuclei, that the entire degeneration passed through the superior peduncle to the opposite red nucleus and thalamus From the roof nuclei no degeneration occurred in the brachium conjunctivum but passed through the hook bundle and fastigio-Deiters bundle to the bulb. Sachs and Fincher (1927), in similar experiments, found degeneration after lesions of the emboliform nucleus to pass as a compact bundle through the superior peduncle.

Experiments on lower mammals are in agreement that the dentate nucleus projects through the brachium conjunctivum (Allen, 1924; Rasmussen, 1933).
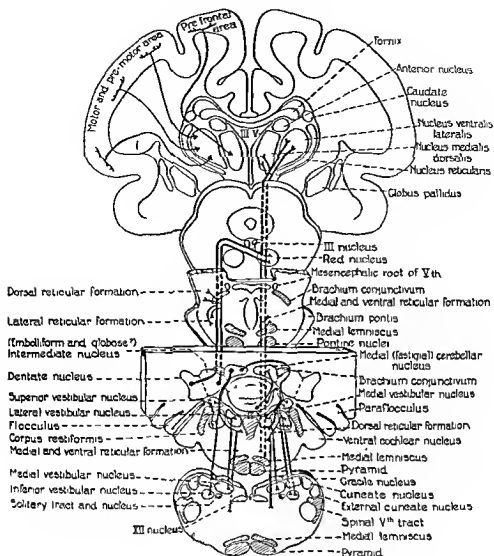
Fig 104b —Scheme to show corticonuclear connections (Reproduced with the permission of Dr Robert S Dow)

Following lesions of the **brachium conjunctivum** degeneration has been followed by the Marchi method to the nucleus ventralis lateralis of the heterolateral thalamus (Crouch and Thompson, 1938b). Walker (1938b) found the same termination in the chimpanzee (fig 104b).

Thalamocortical Projection—There seems to be general agreement that the ventrolateral nucleus of the thalamus projects to areas 4 and 6 (fig 105) of the cerebral cortex (Walker, 1936; Clark and Boggon, 1935).

Thus, the circuit from the **cerebral cortex** to cerebellar cortex and back again to the precentral cerebral cortex is complete. Many of the details
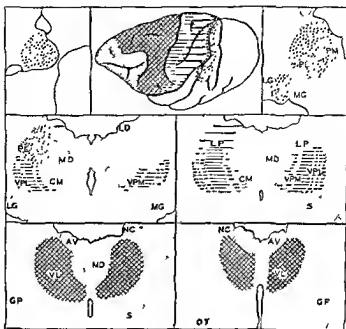
Fig 105a

Fig 105—Diagrammatic representation of the projection from the various thalamic nuclei to various portions of the cerebral cortex Fig 105a Monkey (after Walker, 1938a) Fig 105b Chimpanzee (after Walker, 1938b) Abbreviations AI, nucleus anteroventralis, CM, nucleus centrum medianum, GP, globus pallidus, I, nucleus pulvinaris inferior, L, nucleus limitans, LD, nucleus lateralis dorsalis, LG, corpus geniculatum laterale, LP, nucleus lateralis posterior, MD, nucleus medialis dorsalis, MG, corpus geniculatum mediale; NC, nucleus caudatus, OT, tractus opticus; PL, nucleus pulvinaris lateralis, PM, nucleus pulvinaris medialis, R, nucleus reticularis, S, corpus subthalamicum; T, tectum mesencephali, VL, nucleus ventralis lateralis; VPL, nucleus ventralis posterolateralis, VPM, nucleus ventralis posteromedialis

remain uncertain because of the inherent defects of the Marchi, Gudden, and Nissl technics, but the broad lines are unmistakable.

Electrical Studies

Confirmation of the anatomical findings has recently been obtained by modern electrical amplifying methods.

Dow (1942a) found by single shock electrical stimulation of the cerebral cortex that potentials were evoked in the cerebellar cortex. The most widespread potentials were produced when areas 4 and 6 and the postcentral gyrus were stimulated. From area 8 also potentials were evoked, particularly in the lobulus ansiformis. Stimulation of area 4 caused the most intense disturbance in the median and paramedian lobes and of areas 4s and 6 in the lobulus ansiformis. No difference in the responses in Crus I and
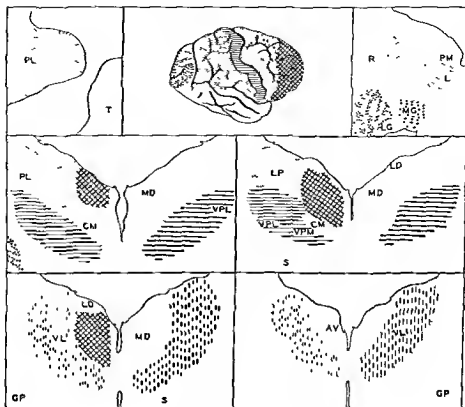
Fɪɢ 105b

(For explanation, see facing page)

Crus II of the lobulus ansiformis could be found, regardless of the area of cerebral cortex stimulated. Electrical stimulation of the pontine nuclei causes potentials to appear in the middle lobe of the vermis, the lobulus ansiformis, the lobulus paramedianus, the paraflocculus, and pyramid, occasionally also in the dorsal part of the culmen (Dow, 1939).

Walker (1937b) has found electrical evidence of the pathway from cerebellar cortex to the cerebral cortex by stimulation in cats with isolated encephalon. Faradic stimulation increased the electrical activity of the cerebral cortex around the cruciate sulcus. Rossi (1912) had shown long ago that stimulation of the cerebellar cortex lowers the threshold of electrical excitation of the motor cerebral cortex. This has been confirmed recently by Moruzzi (1941a) who found that, in cats under chloralose, stimulation of the neocerebellar lobes (Crus I and Crus II—lobulus paramedianus of Bolk and lobulus medius medianus of Ingvar) not only lowers the threshold of the motor cortex to electrical stimulation, but also provokes localized clonic activity and even generalized epilepsy. Morison and Dempsey (1942) found in cats under nembutal that stimulation of the

brachium conjunctivum produces major effects in the motor and "premotor" areas. Adrian (1943) has shown by strychninization of the face, arm, and leg subdivisions of the rolandic cortex that they activate the face, arm, and leg subdivisions, respectively, of the contralateral lobulus simplex and anterior lobe of the monkey's cerebellum.

Scanty though these electrical studies are, their results are in accord with the anatomical findings that there is an important connection between the cerebral and cerebellar hemispheres.

Extirpation Experiments

Even scantier extirpation experiments add their confirmatory data.

Aring and Fulton (1936) found that the tremor which results from removal of the cerebellar hemisphere disappears after subsequent extirpation of areas 4 and 6 of the cerebral cortex, but is accentuated by lesions of 6 alone. Fulton, Liddell, and Rioch (1932) found also that the tremor of decerebellated cats was stopped by subsequent decerebration.

Evidence from Human Pathology

Since the thesis of Turner (1856) many cases have been recorded indicating an essential relationship of the cerebral cortex to the opposite cerebellar hemisphere in man. Most of these cases were crossed atrophies from lesions incurred in childhood. Kononova collected those previously recorded and showed by study of four adult cases (Thomas and Kononova, 1912) that such a crossed atrophy of the cerebellum could occur also from an injury to the cerebral hemisphere during adult life. An extraordinary case of this type has been studied by Bertrand and Smith (1933). The patient, an elderly lady, was kicked in the head by a horse during childhood. The lesions found at necropsy involved the frontal lobe, frontopontine tract, pontine nuclei, opposite dentate nucleus, brachium conjunctivum, and homolateral thalamus.

Descriptions of the corticopontine tracts in man are confused and contradictory. Flechsig (1876) and Dejerine (1901) described fibers arising in the precentral gyrus and passing through the middle part of the peduncle to end in the pontine nuclei. Winkler (1927) states that the frontopontine tract terminates chiefly in the rostral third of the pons about the dorsal nucleus and associated dorsal elements of the peduncular nucleus. Masuda (1914) found that it ramified almost exclusively in the mediodorsal region of the anterior third of the pontine gray matter. The pyramidal tract, insofar as it has a relation with the pons, he found to ramify in the entire length of the pons, most strongly in the middle third. Dejerine (1901)

described also another frontopontine tract from the inferior frontal gyrus and rolandic operculum, stating that it passed through the inner segment of the peduncle as Arnold's bundle. Pfeiffer (1934) believed that these fibers arise from area 44.

A tract first described by Türck is known as the temporopontine tract. Dejerine (1901), Marie and Gudlam (1903), and Rhein (1922) have studied this bundle. Their work indicates that it arises from the posterior part of the temporal lobe adjoining the parietal and occipital lobes. This would explain the fact that Bucy and Kluver (1940) and Rundles and Papez (1938) found no degeneration to the pons after extirpation of the temporal lobe.

Meyer (1907) found fibers from the parieto-occipital region into Türck's bundle by the Marchi method.

The pontocerebellar connections in man are generally agreed to be predominantly crossed with perhaps some homolateral fibers. Masuda (1914) concluded, from the cases he studied in Monakow's laboratory, that the caudal part of the cerebellar hemisphere finds its representation especially in the anterior half of the contralateral pontine gray, and the frontal part in the caudal half. The dorsal pontine gray is connected with the lobulus gracilis and cuneiformis, the lateral gray with the lobulus semilunaris, and the ventral gray with the lobulus cuneiformis, in such a way that the caudal part of the pons is related to the frontal part of the cerebellum and vice versa. Uemura (1917) studied in Monakow's laboratory also an old gunshot wound of the cerebellum and concluded that most of the cells of the ventral pontine gray matter (caudal two-thirds) send their fibers to the lobulus biventer through the ventrocaudal part of the opposite middle peduncle.

That the pontine nuclei are connected primarily with the crossed cerebellar hemisphere is indicated by a number of laborious studies of more or less localized atrophies or hypoplasias of the cerebellum These cases are necessarily not so sharply demonstrative as experimental ones but often involve predominantly those parts of the cerebellum which we have come to call the neocerebellum (Brouwer, 1913; Brun, 1917; Winkler, 1923). The literature up to 1917 was collected by Brun (1925) who also wrote a useful review of all the literature concerning the anatomy, development, and physiology of the cerebellum. It is unnecessary to cite all the subsequent confirmatory cases described. As an example we may note in Brun's case L (Schl) that there was an aplasia of the neocerebellum with normal development of the paleocerebellum (flocculus and vermis). The dentate nuclei were represented only by small nests of cells, and there was total aplasia of the ventral and lateral gray matter of the pons in all sections. Other cases vary only in details.

Degenerations following lesions of the superior cerebellar peduncle in man follow much the same course as in lower vertebrates. Uemura (1917) gives the preceding literature and noted in his case of gunshot wound that the fibers of the brachium conjunctivum went through the red nucleus and ended in the opposite thalamus.

That the ventrolateral nucleus of the thalamus projects to the precentral gyrus in man is probable, but the inadequacy of the human pathological material for the exact determination of such problems is evident from such articles as that of Fukuda (1919) who, after a laborious study of 13 cases from Monakow's laboratory, could conclude vaguely only that the most oral part of the lateral thalamic nucleus seems to have its optimal representation in the caudal part of the frontal lobe. That the relationship in man is similar to that established for the macaque is made more probable by the results of experiments in the chimpanzee. Meier-Müller (1919) found, after a cortical extirpation of the "elbow" region of the precentral cortex 16 months previously by Sherrington and Graham Brown, that there was atrophy only in the lateral nucleus of the homolateral thalamus. Walker (1938b) found that the nucleus ventralis lateralis (anterior half of the lateral nuclear mass) projects to the motor and premotor areas.

The Rubro-Olivary System

Two other gray masses in the brainstem are intimately involved in the cerebro-cerebellar relationship—the red nucleus and the inferior olive. Their connections are still more obscure than those of the pontine nuclei, but the projection of the inferior olive on the cerebellar cortex has been worked out in some detail. Pathological studies (Holmes and Stewart, 1908; Zimmerman and Brody, 1933) indicate that specific lobes of the cerebellum are related to definite portions of the olivary complex, and such a definite relationship has been proven for the rabbit and cat by the careful experimental study of Brodal (1940). Dow (1939) attempted to check these results by electrical stimulation in the cat but found that electrical stimulation in the neighborhood of the inferior olive apparently caused synaptic activation of the whole of the olive, since action-potentials appeared throughout the cerebellar cortex.

Hatschek (1907) showed that the red nucleus has a magnocellular and a parvocellular portion and that the latter increases in importance in higher mammals. One would expect, therefore, to find a prominent corticorubral tract or tracts in primates, but, although frontorubral fibers have been described in man by Monakow (1909), LaSalle Archambault (1914), and others, Levin (1936) was able to conclude from his studies on the macaque

only that probably such fibers pass from both areas 4 and 6 in small numbers to the red nucleus. According to Mettler (1935b) fibers go to the red nucleus from the cortex just posterior as well as anterior to the central sulcus and also from the temporal region and from the middle and inferior frontal gyri. In addition, Mettler (1935c) maintains that fibers go directly to the inferior olive from the ventral portion of the precentral gyrus and from the parietal region.

Fibers pass to the red nucleus from the dentate nucleus, and a rubro-thalamic tract accompanies the dentato-thalamic fibers to the anterior part of the ventral nucleus of the thalamus (C. Vogt, 1909). Other efferent projections are complicated and confused (Winkler, 1929).

In addition to the cerebellar connections, the inferior olive receives afferent fibers from the spinal cord and a large descending tract which is supposed to arise from the thalamus. Winkler (1933) has described a strato-olivary tract and favored a pallido-rubro-olivary tract. Papez and Stotler (1940) have described similar tracts.

However confused and uncertain is our knowledge of the connections and functions of the red nuclei and inferior olives it is established that they develop large new portions simultaneously with the development of the cerebral hemispheres and cerebellar hemispheres and that they are intimately connected at least with the latter. Moreover, the inferior olives atrophy along with the neocerebellum and pons in the systemic disease known as olivo-ponto-cerebellar atrophy (Dejerine and Thomas, 1900) In this disease the dentate nucleus is sometimes atrophied (Davison and Wechsler, 1938), and even the red nucleus (Lejonne and Lhermitte, 1909) although it is more likely to suffer in the crossed cerebro-cerebellar atrophies (Mingazzini, 1908).

Significance of the Cerebro-Cerebellar Connections

The pyramidal tract is the principal efferent pathway for voluntary motion. The circular connection arising from the same cortical areas and involving the cerebellar hemisphere reminds one of the feed-back mechanisms well known to engineers. It seems logical to suppose, therefore, that the neocerebellum exercises some controlling influence on voluntary motion. The cerebellar cortex being more uniform in structure than the six-layered isocortex of the cerebrum suggests further some fundamental influence common to all the cerebellar cortex, the points where it is exerted depending on the efferent connections of the various portions of that cortex.

The effects of lesions of the neocerebellum in man have long been known; they have been clearly described by Holmes (1917). The symp-

toms are on the same side of the body as the lesion, affect both arm and leg, and affect the arm more than the leg. The arm is limp and, if shaken, the parts flap loosely about. The muscles feel flabby; the limb is, therefore, said to be atonic. Moreover, there is a slight weakness and the limb tires easily; there is, in other words, an asthenia. But the most striking symptom is the irregularity of voluntary movements. These cause the limb to move jerkily and irregularly and to fail to reach its goal accurately. The limb may fall short or overreach the mark. Rapid alternate movements cannot be made well. These various disorders of coordination of voluntary motion are known as asynergy. There is also a tremor, characterized by coarse terminal irregularities of movement not increased by closing the eyes.

These symptoms are not so pronounced or enduring in macaques; hypotonia and disturbance of skilled movements result from removal of the cerebellar hemisphere (Botterell and Fulton, 1938a), but tremor is scarcely evident unless the dentate nucleus be involved. In chimpanzees the symptoms are more pronounced and enduring in both arm and leg and associated with noticeable tremor of voluntary movements (Fulton, 1938).

Results of lesions of the neocerebellum indicate, as one would expect from the anatomical connections, that its influence is exerted mainly on voluntary motion, the impulses initiating which leave the cerebral cortex over the pyramidal tract mainly from areas 4 and 6. Moreover, the results indicate further that this influence in some way regulates such movement, enabling it to take place in a smooth measured manner adequate to its purpose.

Babinski first suggested that the cerebellum accomplishes this regulation by acting as a brake (Babinski, 1906). It is obvious that he was thinking particularly of the activities of the part we now distinguish as the neocerebellum (Babinski and Tournay, 1913). Walshe (1927) insisted on the essentially cerebral origin of cerebellar asynergy and argued that it is solely voluntary movement which is dependent on cerebellar activity. It is certainly true for the neocerebellum, as he believed, that the secret of cerebellar activity is to be sought in a close functional relationship between cerebral motor cortex and cerebellum, but Ectors (1942) has shown that, for those fundamental reflex activities of brainstem and cord which subserve the elements of coordination, the paleo- and archicerebellum exert the same braking action to overcome and regulate their inertia, i.e., that property which bodies have to persist in their state of rest or movement until some external force alters it. And this theory can be reconciled with

Sherrington's (1906) conception of the cerebellum as the main ganglion of the proprioceptive system, since the older parts of the cerebellum exert this braking influence on the essential proprioceptive mechanisms in the brainstem, which Magnus (1924) has so brilliantly analyzed.

The archicerebellum (flocculonodular lobe) is connected primarily with the vestibular system and its associated equilibratory mechanisms (Dow, 1938b); the paleocerebellum with those spinal mechanisms (Bremer, 1935) which depend on stretch reflexes in the limbs—in birds mainly the wings, in man mainly the legs—for the maintenance of postural tonic contraction. This tonic supportive contraction must be modified to make voluntary motion effective, the modification being produced by efferent paleocerebellar projections (Nulsen, Black, and Drake, 1948; Snider and Magoun, 1948) simultaneously with the production by the pyramidal projection of voluntary contraction, which is itself regulated (braked) by the influence of the neocerebellum (Ectors and Marchant, 1946).

Chapter XI

AUTONOMIC FUNCTION

Margaret A. Kennard, M.D.

Associate Professor of Experimental Surgery
University of Oregon Medical School[1]
Portland

OUTLINE OF CHAPTER XI

Autonomic Function

AUTONOMIC FUNCTION

DURING THE MANY CENTURIES in which man has been speculating as to how it is possible for him to speculate, there has been no thoroughly satisfactory concept of the relation of mind and matter. It is not surprising, therefore, that there is relatively little known about the functional relations of the cerebral cortex, the integrator of all volition, with the autonomic or involuntary nervous system, regulating bodily function. Early literature on the subject is at once slight, vague, repetitive, and contradictory, in contrast to that on somatic function which shows long years of meticulous and methodical development.

Yet, after studying the cortico-autonomic literature, one is left with the conviction that there is plenty of evidence for a specific and localized effect of the cerebral cortex on the involuntary nervous system. It is overshadowed, however, both by the relative importance of the somatic functions of the *cortex* and by the relative importance of the autonomic functions of the *hypothalamus*. In recent years, in particular, the development of electro-physiological methods, such as cortical stimulation, measurement of galvanic skin response, and oscillographic recordings, has made possible many discoveries. The recent progress in psychology and psychiatry has also been of use in this field.

For earlier literature on the subject the reader is referred to the extensive work of Bechterew (1908-1911), one of the few early investigators who devoted more than passing time to the subject, to the papers of Danielopolu and his associates (1922, 1926, 1931), and to Spiegel (1932). There are reviews of various phases of the subject by Fulton (1934b, 1936a, b), Foerster (1935), Kennard (1937), Dunbar (1938), and Langworthy, Kolb, and Lewis (1940) which make extensive citation of early literature unnecessary. The recent review by Miller (1942) on *Central Autonomic Regulations in Health and Disease* has an excellent presentation both of cortico-autonomic relations and of the present state of knowledge of other central autonomic regulation, notably the hypothalamus. The present review, therefore, will be limited largely to discussion of more recent articles which are useful in the delineation of the present concept of cortico-autonomic function.

Clinical Evidence of Cortico-Autonomic Interrelations

Evidence of cortico-autonomic interrelations may be found in every branch of the involuntary nervous system. Common observation of normal man has produced many such examples. Thus, a thought or idea which

has an emotional content may evoke changes in the circulation, such as the local phenomenon of pallor or blushing, or more general changes in blood pressure or heart rate. Sweating, pupillary dilatation, gastrointestinal discomfort, or bladder disturbances may appear also.

It is not uncommon to find in certain individuals that there is voluntary control of some of these functions usually thought of as autonomic—pupillary (Bechterew, 1895), pilomotor (Maxwell, 1902; Chalmers, 1904; Brickner, 1930), and vasomotor changes both generalized (Kennard, 1937) and focal (Mitchell, 1884) being among the most common. Hypnosis, trances, and ordinary sleep are all states related to alterations in both somatic and autonomic function in which interrelations must occur.

"Abnormal" clinical subjects, some with known lesions of the cerebral cortex, may have characteristic autonomic changes. The most usual are those within the vasomotor system. There is one common type of patient having, invariably, a tendency to cold hands and feet, and palpitation of the heart, and a marked lability of vasomotor system who shows signs varying from mild strain or anxiety states to more severe symptoms of psychological disturbances The same type of person often shows symptoms of gastrointestinal distress varying in degree and kind from distention and "bloating" to pain or definite signs of gastric or duodenal ulcer or colitis (Fulton, 1936a; Watts, 1935; Masten and Bunts, 1934).

Changes in the skin are common in certain patients and directly related to emotional stress Excessive sweating may occur also Less frequent, but still not unusual, are eruptions of the skin. Urticaria, together with asthma and the other manifestations of allergy appear in some individuals only at times of stress and in response to psychological stimuli. Such chronic skin diseases as psoriasis are known to be influenced in the same way (Bernstein, 1938).

There is some peculiar and specific relationship between the voluntary motor system and emotion. In normal individuals coordination of voluntary movement is often less smooth under stress. Tremor appears in the same conditions. In epileptics, anxiety, fatigue, or often some other type of strong emotion, may induce an attack. Both spasticity and tendon reflexes are augmented during excitement, and this has been found to be directly related to the sympathetic adrenal hormones (Jacobsen and Kennard, 1933).

Hemiplegia is very often accompanied by unilateral changes in the autonomic system And, although in man it is usually impossible to prove that the lesion is purely cortical, the evidence is that such is occasionally the case. It is definitely so in experimental animals.

Immediately following the appearance of a hemiplegia the affected extremities of a patient are most often pinker and warmer than those of

the normal side. Later, in the space of a few days or weeks, they become paler and colder, and the patients then complain that there is increased sweating of the affected limbs and that they are constantly cold (Hitzig, 1876; Horsley, 1889; Bucy, 1935a; Kennard, 1935a, 1936a). This change may last for the duration of life in an individual or may disappear with improvement in the motor paresis.

There is sometimes increased permeability of the capillaries with resultant edema. This appears most often in patients in whom there are signs of cardiac decompensation or some other factor which of itself produces a tendency to edema. It was discussed by Allen in 1899 and by Deumié in 1907 with citation of a number of cases. Recently a patient was observed by the author who showed this to a striking degree:

This individual, aged 45, was a known hypertensive who had been in the hospital twice before because of early signs of decompensation. Because of this decompensation also he had been at home and in bed for some months previous to the final admission. He was then brought to the hospital because of sudden onset of left hemiplegia during the night before admission. He was found to have a complete flaccid left hemiplegia to be nearly comatose and to have extreme cyanosis and pitting edema of all extremities particularly of the legs. At the time of admission the edema was equal on the two sides. With digitalis the condition of the patient was improved somewhat during the next two weeks, but, in that time, in spite of the fact that he was kept constantly lying on his right side or back and never on the left side, the edema entirely disappeared from the right but remained nearly as marked as on admission on the left. Very large decubitus ulcerations appeared extremely rapidly on the left buttock, heel and calf. There were none on the right side. It was obvious that, on the side affected by the hemiplegia there were some vasomotor changes which increased the permeability of the capillaries there. At autopsy, this patient showed a fairly discrete vascular lesion affecting the right internal capsule.

Experimental Evidence of Cortico-Autonomic Interrelations

All of the above phenomena which appear clinically have been investigated experimentally, as have other involuntary functions related to both somatic and autonomic function, such as respiration and shivering.

Gastrointestinal Tract—Both intussusception (Watts and Fulton, 1934) and gastric ulcers (Keller, 1936; Mettler, Spindler, Mettler, and Combs, 1936) have appeared in experimental animals (monkeys, dogs, and cats) following cortical ablations, and there is evidence that the area most closely related to this function is area 6 in the frontal cortex (see Brodmann map, fig. 95, p. 249) (Fulton, 1936b).

Confirming and amplifying this, Hesser, Langworthy, and Kolb (1941), utilizing a balloon-tambour-air-water system, found that, in the cat, after removal of cerebral motor cortices, gastric activity was definitely altered. There was greater persistency, constancy, and strength of stomach contractions along with increased tone through distention. Similar but less marked changes appeared in the oesophagus. It was suggested that the changes were due to removal of regulating influence on the gastrointestinal tract.

Sheehan (1934) found changes in gastric motility on stimulating area 6, and Bailey and Sweet (1940), stimulating the orbital surface of the frontal lobe, produced inhibition of gastric tonus in both cats and monkeys.

Circulation—Investigations of changes in circulation have been of various types.

(1) Blood pressure changes in response to cortical stimulation have been recorded by many observers. The paper of Howell and Austin (1899–1900) was one of the first on the subject. The usual change in response to stimulation is that of increase in blood pressure (Dusser de Barenne and Kleinknecht, 1924; Crouch and Thompson, 1936). Stimulation of the frontal lobe most often produces such changes. In contrast Darrow (1937) reports consistently low blood pressure and low galvanic skin responses in psychotic patients, particularly those having "anxiety symptoms."

More recently (1942) Darrow has given further evidence of intimate cortico-autonomic connections. By intricate simultaneous recording of electroencephalogram, galvanic skin response, blood pressure, and respiratory rate he has found that decrease in alpha rhythm and increase in beta rhythm appears on excitement and coincidental with autonomic effects But a rise in blood pressure may also appear, which tends to be associated with increased alpha rhythm, thereby exerting, according to the author, a homeostatic influence.

(2) Vasomotor changes as a result of cortical changes have been measured Pinkston, Bard, and Rioch (1934) found, after removal of portions of the forebrain of dogs and cats, that there was a chronic vasodilatation and absence of true polypneic panting. There was a suggestion that the control of temperature in these animals was located in the contralateral sensorimotor area. In 1936 measurement of skin temperature in monkeys before and after removal of portions of the cortex (Kennard, 1936a) demonstrated that vaso-constriction appeared contralateral to lesions restricted to the premotor cortex (area 6 of Brodmann, fig. 93, p. 249). In man (Kennard, 1937) lesions of internal capsule or cortex produce similar inequality between skin temperatures of the two sides of the body.

Vasomotor changes such as produce edema in the hemiplegic human were found in monkeys by Green and Hoff (1937) who stimulated the cerebral cortex and recorded plethysmographically the volume of limbs and kidney. Stimulation of areas 4 and 6 produced diminution in kidney volume in anesthetized monkeys with or without curarization. This effect disappeared with denervation of the kidney. Their conclusion is that the changes occur normally concomitantly with movement of the limbs and thereby facilitate blood supply to active muscular tissue.

There is much discussion in the literature as to whether the skin temperature change is primary or secondary to disuse and possibly to atrophy.

The evidence seems to be that it is primary: it appears in man and monkeys immediately after cortical insult, usually to area 6; it may be present when paresis is either minimal or absent, and when there is no atrophy; *vasodilatation* is usually first seen during the stage of profound paralysis.

Sweat Secretion—Changes in perspiration were studied in humans by Guttmann and List (1928) and by Guttmann (1935). These authors observed degrees of sweating after application to the skin of a starch-iodine preparation which turns blue with moisture. Their startling photographs of patchy blue areas of sweat localized to half or part of the body are known to many. The galvanic skin reflex, another method of measuring sweat production, is altered after cortical extirpation in cats (Schwartz, 1936) and in man (Darrow, 1936, 1942) coincidentally with cortical changes. Increased sweating usually appearing contralateral to cortical lesions of the frontal lobe. Stimulation of the motor area of the cat was also found to alter galvanic skin response on the contralateral side (Wang and Lu, 1930). Bucy and Pribram (1943) observed localized sweating in association with localized convulsions of the face in a patient with a tumor beneath the "face" area of the precentral gyrus.

Pupillary Changes—It is very well known that pupillary changes appear in response to cortical stimulation when the stimulus is applied to the area from which eye or lid movements can also be elicited (see Chapter XII). Focal areas for dilatation (Wang, Lu, and Lau, 1932) and constriction (Barris, 1936) have been described.

Ury and Oldberg (1940) studied the cortical effects on the pupil by an ingenious method wherefrom they were able to postulate a general scheme of the mechanism of pupillary activity. The threshold to pain was studied in cats trained to certain conditions. This, as shown by pupillary dilatation, was lowered by massive cortical lesions but was not altered by lesions confined to sensory or sensorimotor cortex. Lesions of either the area capable of inhibiting extrapyramidal movements or of the temporal lobe resulted in dilatation of the pupil. On the basis of their experiments the authors postulated that the pupillary change is due to removal of inhibition rather than to stimulation of the sympathetic system.

Bladder Function—This has been thoroughly investigated by Langworthy (Langworthy and Hesser, 1936) and has been so fully discussed in his book that analysis of the literature on the subject is here useless (Langworthy, Kolb, and Lewis, 1940).

Of changes which appear in man as a result of cortical disturbances these authors say:

Patients with acute lesions injuring the cortico-efferent pathways often have vesical retention during the period of shock. Later they develop urinary symptoms related to loss of function and release of function. Lack of ability to start micturition volun-

tardy or to control the urinary urge leads to incontinence and may be attributed to loss of function Urgency and frequency of micturition are dependent on release. The stretch reflex is hyperactive and the bladder

They summarize the central nervous control of the bladder as follows:

Both by stimulation and by extirpation experiments there is evidence of a midbrain control of micturition such as Barrington suggested Without an exception, all reports are in agreement that vesical responses may be obtained from the lateral portions of the periventricular gray matter in the midbrain Bladder contractions have been obtained from areas rostral to the midbrain One group described them as elicited from the internal capsule, another feels that the responses are due to stimulation just lateral to the ventromesial portion of this structure Cortical stimulation has given results which seem to be less easily repeated and

contracts forcibly upon a smaller volume of fluid than formerly There is difficulty in passing a catheter through the spastic external sphincter

less easily obtained than those from lower centers Furthermore, they appear to differ in their much greater latency However, the responses have always been obtained from portions of the sigmoid gyrus (the motor area) in cats and dogs, and the localization given by various workers is much the same The results of cortical extirpation indicate that the animal micturates automatically He passes the same volume of fluid regularly, suggesting there is no longer any cerebral control which may voluntarily modify the ability of the bladder to hold varying amounts of fluid

Pilomotor Changes—A very careful analysis of an individual capable of voluntary piloerection has been carried out by Lindsley and Sassaman (1938). In this man voluntary erection of body hairs was accompanied by increase in heart rate and respiration, by dilatation of pupils and increased electric potentials over areas possessing sweat glands. Preceding and during this period electroencephalographic readings made from the skull above area 6 showed a significant change. No such change could be recorded above other cortical regions.

In this laboratory it is a common observation that in monkeys and chimpanzees ablation of area 6 bilaterally produces a marked and persistent piloerection. There is, however, no unilateral effect after unilateral ablation of area 6. This is not surprising also as area 6 is known to have marked bilaterality of function in other respects also. No piloerection appears after ablation of any other cortical region.

Shivering—Aring (1935) reported that monkeys deprived of area 4 showed increased shivering and a low threshold to cold; that lesions elsewhere in the cortex produced no such change; and that antero-lateral cordotomy abolished shivering. Uprus, Gaylor, and Carmichael (1935) made the same observation in man: that cordotomy abolished shivering, but that section of the pyramidal tracts had no such effect. They concluded that shivering must therefore be mediated through extrapyramidal pathways and be "inhibited" by the pyramidal influence.

In corroboration of this, Pinkston, Bard, and Rioch (1934) found excessive shivering in cats deprived of motor cortex, and it is another common observation in this laboratory that monkeys, following ablation of area 4 unilaterally, but to much greater degree if the lesion is bilateral.

show excessive movement during shivering. After unilateral lesions the excessive movement is only on the contralateral side. The same animals have other forms of exaggerated movement, particularly of the jerking and jumping "startle response" to fear and rage which is characteristic in milder form in the normal macaque. It is probable that the excessive response to cold and to fright or rage is similar and part of the generalized over-reactions which appear together with paresis following cortical trauma to motor areas. There is a similar over-reaction in movements which have no emotional background, for fine purposeful finger movements are always executed less smoothly after removal of area 6. Even in this instance, however, emotional excitation of any type always accentuates the disability.

Respiration—Like shivering respiration is an involuntary automatic function which involves striate muscles and which might therefore be expected to be mediated through the cerebral cortex. However, it is well known both that respiration may be carried on by decorticate preparations, and that lesions in the midbrain may cause cessation of this function

But cortico-autonomic influence is also present though slight and has been studied by various observers (Bucy and Case, 1936, 1937; Smith, 1938). Bailey and Sweet (1940), stimulating the orbital surface of cats and monkeys, found an area inhibiting respiration, which also effects a rise in blood pressure and a decrease in tonus of the gastric musculature. Confirming these cortical effects on respiration by determining the afferents to the cortical area Bailey and Bremer (1938) caused an increase in electrical potentials of the orbital surface of the frontal lobe of cats by stimulating the vagus nerve

Psychological Data—Use of the conditioned reflex in experiments has brought out a mass of material related to cortico-autonomic interaction. The "psychic" secretion of saliva or gastric juice, as demonstrated by Pavlov, is known to be dependent on the cortex, and conditioning of pupillary response is similarly well established (Hudgins, 1933).

Recent attention has been drawn to the "experimental neuroses" produced in sheep and other laboratory animals in which profound autonomic changes take place together with behavioral changes, as a result of frustration (Anderson, Parmenter, and Liddell, 1939; Anderson and Parmenter, 1941; Liddell, 1941) The paper of Anderson, Parmenter and Liddell is summarized by the authors as follows:

Sheep in which an experimental neurosis has been developed reveal, upon examination, a cardiac disorder which is characterized by a rapid and irregular pulse and by extreme sensitivity of the heart's action in conditioned and other stimulation Rapid increases of rate occur in response to mildly startling stimuli which have no effect upon the pulse of normal sheep Spontaneous variations of rate are observed both in the barn and in the laboratory Conditioned stimulation produces a considerable and long continued increase in pulse rate associated with premature beats and sometimes with coupled rhythm

The syndrome in these animals is startlingly like that found in humans under stress or those who display the characteristics of an anxiety neurosis.

Reflex conditioning to sound has been shown by Bykov (1938) to result in increased visceral activity. A related phenomenon is the production of epileptic seizures in response to repetitive sound in rats (Humphrey and Marcuse, 1941; Lindsley, Finger, and Henry, 1942). Other phases of such psychosomatic problems will be found in the review of the subject by Liddell (1941) and in the *Journal of Psychosomatic Medicine*. Their ramifications are too specialized and too extensive to be dealt with here.

The procedure originated by Moniz and elaborated by Freeman and Watts (1942) of severing the fiber tracts from the prefrontal areas of patients with various forms of psychotic or neurotic manifestations has contributed a number of points related to psychosomatic function and the autonomic system. These authors state, that in the majority of such patients, preceding operation, the hands and feet were excessively cold, but that this symptom usually disappeared after operation. Furthermore, many of these individuals, operated on under local anesthesia, vomited during or at the close of the operation, and more than half of them had urinary incontinence for a few days post-operatively. Rectal incontinence also appeared occasionally. After operation, marked increase in appetite and gain in weight are the usual occurrence.

Gross ablations from the cortex of animals have produced certain "behavioral changes" which give indication both of the autonomic function of the cortex and of the function of the hypothalamus in the absence of cortex. The well-known decorticate animals of Bard (1928, 1934, 1939) exhibit excessive responses of rage together with piloerection, extrusion of the claws, and spitting (in cats). A similar but less marked emotional response may appear when the forebrain alone is removed (Spiegel, Miller, and Oppenheimer, 1940; Magoun and Ranson, 1938).

Increase in activity, distractibility, and states of excitement have been found in many forms of laboratory animals after frontal ablations, but these have not been shown to be associated with any other very marked autonomic changes (Kennard, Spencer, and Fountain, 1941). The hyperactivity which appears consistently after total removal of the frontal association areas has been produced by Ruch and Shenkin (1943) by small bilateral lesions confined to the orbital surface of the frontal lobes.

The alterations of behavior as described by Klüver and Bucy (1939) which follow bilateral temporal lobectomy are also of an "affective" nature, but there are no obvious organic autonomic changes associated with them, as there are with lesions of area 6 of the frontal lobe.

Sleep—The cortical changes which appear during sleep should be mentioned, since it is well known that there are decided changes in pupils,

heart-rate, respiration, and the vasomotor system as this takes place
Whether sleep can ever be called either a diencephalic or a cortical phe-
nomenon is doubtful. That it does affect consciousness and "volition" is
certain, and, if electroencephalograms are records of cortical activity, which
is not certain, then sleep has definitely to do with the cortex, for there are
marked changes in the electroencephalogram during sleep (Rowe, 1935;
Davis, Davis, Loomis, Harvey, and Hobart, 1938; Loomis, Harvey, and
Hobart, 1938; Blake, Gerard, and Kleitman, 1939). Anesthesia similarly
produces profound changes in the electrocorticogram (Derbyshire, Rempel,
Forbes, and Lambert, 1936; Forbes and Morison, 1939; Beecher and Mc-
Donough, 1939).

Discussion

Although there is much in the nature of this cortico-autonomic inter-
play which is not yet understood, functionally it is now evident that two,
and possibly three, parts of the cerebral cortex of man and other primates
have direct influence on the involuntary nervous system.

First, the motor areas of the frontal lobe—area 6, and to a less extent
areas 8 and 4—influence the circulation, pupil, bladder, gastrointestinal,
and pilomotor systems

The second focal area which may affect autonomic function is the
frontal pole Here bilateral ablation may affect respiration, gastric motility,
or blood pressure The orbital surface of the frontal lobe is that most
directly concerned with these functions. General behavior, or response to
emotional environmental conditions may be altered by lesions here.

Third, the temporal lobe is beginning at the present state of our knowl-
edge to have attributes which connect it with the autonomic system. Clin-
ically it is known to be the area related to the complex mental processes
concerned with sound and smell, and its bilateral removal in monkeys
produces behavioral changes possibly related to smell or sound. It may
well be, therefore, that the experimental neuroses and epilepsy induced
by sound are due to functional or organic disturbances in the temporal
lobe, just as the "anxiety states" of man may be related to the frontal
poles. Finally, as the hypothalamus has been shown to be the area of the
central nervous system most strongly influencing the autonomic system,
and as both the hypothalamus and temporal lobe are concerned with olfac-
tion, it is very probable that there are both anatomic and functional con-
nections between the two which will be defined in future research.

Anatomic evidence of the fiber tracts forming cortico-autonomic con-
nections and, in particular, cortico-hypothalamic connections, is slight.
Such extensive works as those of Kappers, Huber, and Crosby (1936) or
of Rioch (1929), dealing in detail with thalamic and hypothalamic nuclei,

make no mention of cortical connections with the latter. In fact, the hypothalamic connections are said to be largely with the olfactory system. Levin (1936), investigating the efferent fibers from the frontal lobe of monkeys, found numerous thalamic connections but none to the hypothalamus. But Mettler (1935b) saw some fibers passing from the frontal lobe to the periventricular region of the hypothalamus in the same species. Hunsicker and Spiegel (1933-1934) sectioned the pyramidal tract in some cats and the extrapyramidal, below the hypothalamus, in others. In each case cortico-autonomic effects on pupil, blood pressure, and bladder were present after operation. The conclusion of the authors was that impulses must be mediated via both tracts.

In examining the literature prior to writing this review, it has seemed to the author that great developments have taken place in knowledge of cortico-autonomic function during the past five years. A review of the same subject written in 1937 could report only isolated and often unrelated findings which, although indicative of cortical influence on involuntary function, gave only a suggestion of the interrelated systems as a whole. Today, it is possible to state that there is a cortical influence mediated largely from the frontal lobe, and possibly from the temporal, which affects all branches of the autonomic system in the same way; that there is some cortical localization of function, especially of the pupil, but that it is less definite than that in the somatic system; and that sympathetic and parasympathetic systems alike are affected by the cortex.

In addition it is possible to speculate on the nature of the cortical influence. This has been discussed by many authors, most of whom agree with the opinion so clearly expressed by Langworthy and his associates—that the cortical function is one of control or regulation of the finer autonomic adjustments, and that its absence removes "inhibition" and results in over-reaction or spasticity.

It is also clear that cortical influence on the autonomic system is far less pronounced than that of the hypothalamus, and here two additional bits of information contribute to our concept of cortical function. First, many autonomic reflexes, such as the psychic secretion of saliva or gastric juice, are known to be conditioned and dependent on cortex; and second, there are other reflexes, such as those which increase limb volume in response to stimulation of area 4, which are somatic cortical adjustments.

From these data the most probable concept of the mode of regulation of autonomic function by the central nervous system is that the cerebral cortex integrates all conditioned and learned reactions which are part of the bodily adjustments to somatic cortical processes, but that all other reactions of the involuntary nervous system are mediated solely below the cerebral cortical level.

Finally, the accumulation of evidence on cortico-autonomic function points to a focal representation on the cortical surface which is very similar to that of the somatic representation and which exists to some degree in the cat, dog, monkey, and man. Admittedly, the cortical foci are less definite in the autonomic than in the somatic sphere, but so also is all autonomic activity more diffuse in nature than is somatic. As is shown in fig. 106a, in the monkey, cortico-autonomic representation lies mainly in a band extending along the rostral border of the motor areas and lying between these and the frontal areas which are known to relate to such affective functions as "behavior," "personality," and the more complex emotional reactions. Within this band cortico-autonomic activity is focally integrated with somatic.

In area 6 (fig. 9, p 17, and fig 95 p 249), lying mesially, are the complex somatic postural adjustments of limbs and trunk. Here also are represented pilomotor, sudomotor and vasomotor activity, all autonomic functions which concern limbs and trunk. Bilateral removal of area 6 in the monkey always results in permanent piloerection, and unilateral lesions in monkeys and man cause changes in sudomotor and vasomotor activity. Furthermore, there is some focal autonomic representation within this region, because lesions producing paresis of arm or leg are accompanied

Fig. 106a—Sketch of brain of *Macaca mulatta*, showing somatic and autonomic focal representation. We are indebted to Dr Wendell J S Krieg Professor of Neurology and Director of the Institute of Neurology, Northwestern University, Chicago, for this drawing

by changes in skin temperature and sweat secretion in that extremity only (see p. 372).

Area 8 (figs. 9 and 95), which somatically represents conjugate deviation of the head and eyes, has an autonomic representation for the eyes also (see Chapter XII). Here stimulation may produce either dilatation or constriction of the pupil, and ablation of area 8 from one side is followed by lachrymation of the contralateral eye.

In area 44 (fig. 106a) lies the somatic motor representation for face jaw, and mouth and, closely adjacent, the cortical representation of taste which extends rostral from the central sulcus within area 3. In this same area salivation has been produced by stimulation. Recently Bucy and Pribram (1943) have reported a case in which a glioma lying beneath area 44 and the lower part of area 6 produced localized convulsions of one side of the face and localized perspiration in the same region. Extending over onto the orbital surface, lies the representation of the vagus nerve already discussed (Bailey and Bremer, 1938). The lower part of the precentral motor cortex, areas 4, 6, and 44 (frontispiece and fig. 9, p. 17), represents the somatic portion of the gastrointestinal tract—lips, tongue, and pharynx—while the adjacent region of the lateral rim and orbital surface represents the visceral portion of the same system—the stomach and intestine. Respiration and cardiac function, also vagal in part, may be altered by stimulation in the same region. In particular, the findings of Smith (1938) lend emphasis to this theory. He records that, in the monkey, the region in which respiration is *slowed* by stimulation is that here described as representing vagus but that a region also exists which when stimulated will produce *acceleration* of respiratory rate. This latter lies, as would be expected according to this plan of focal representation, near the midline in area 6, i.e., in the region in which there is also somatic representation of the trunk musculature.

Such a concept, even though it be indefinite in detail, of a focal anatomical representation within the cortico-autonomic system, lying interlaced with a more sharply delimited focal meshwork of somatic representation, simplifies the structural basis for the physiological interactions of these systems. Furthermore, once the experimental data have been established, the site of this cortico-autonomic band is most reasonable, since the representation of the cortico-autonomic system thus is bounded by area 4, which is concerned with "voluntary" motor activity; by the hypothalamus—chief effector for the autonomic system; and by the frontal association cortex, wherein, according to the doctrine of Hughlings Jackson, lie the final and highest centers of the nervous system.

Chapter XII

THE FRONTAL EYE FIELDS

Wilbur K. Smith, M.D.

Associate Professor of Anatomy
University of Rochester School of
Medicine and Dentistry
Rochester, N. Y

OUTLINE OF CHAPTER XII

The Frontal Eye Fields

THE FRONTAL EYE FIELDS

MOVEMENTS OF THE EYES constitute an essential part of the mechanism of vision. It is, therefore, not surprising to find that the fundamental and phylogenetically old mechanism governing these movements is situated in the mesencephalon and adjacent regions of the brain stem. The arrival there of nerve impulses initiated by excitation of the retina, such as occurs from movements of objects or flashes of light, causes a reflex deviation of the eyes toward the source of the stimulus. This deviation of the eyes is normally accompanied by turning of the head in the same direction, thus considerably increasing the range of the rather limited movement which the eyeballs themselves are able to execute. Not only is the eye-movement mechanism affected by visual impulses, but strong excitation of the auditory apparatus also excites a response similar to that produced by visual stimulation. In addition, eye movements are influenced by the vestibular apparatus with which the eye-muscle nuclei are connected by definite nerve pathways, thus forming an important part of the righting-reflex mechanism.

The results of excitation of the various pathways in the brain stem which affect the eye-movement mechanism emphasize the fact that in animals with binocular vision eye movements are essentially bilateral in nature, a necessary corollary of the law that for normal vision the visual axes of the eyes must be so arranged as to permit the image to fall upon corresponding parts of the two retinae.

Following what appears to be a general rule of imposing its powers of regulation and coordination upon mechanisms situated lower in the brain, the cerebral cortex has assumed the role of influencing ocular movements, and a region in the frontal part of the brain has been endowed with this special function. It is a well-established fact that this region when electrically excited responds with movement of the eyes, usually accompanied by movement of the head occurring simultaneously with other responses such as opening of the eyes and dilatation of the pupils. Ablation of this region in monkeys and anthropoid apes causes marked alterations in function, and lesions of it in man produce symptoms which vary according to whether the process is irritative or destructive.

Soon after Fritsch and Hitzig (1870) demonstrated that the cerebral cortex was responsive to electrical stimulation, Ferrier stimulated the cerebral cortex in a variety of mammals, and in 1874 reported the discovery of a region in the frontal part of the brain in monkeys from which ocular responses could be elicited. This study was followed by re-

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ports of the results obtained by electrical stimulation or ablation of this region in different species of monkeys by many investigators, including Ferrier and Yeo (1884), Schäfer (1887), Horsley and Schäfer (1888), Beevor and Horsley (1888), Mott and Schafer (1890), Sherrington (1893), Russell (1894), Jolly and Simpson (1907), C. and O. Vogt (1907, 1919), Levinsohn (1909), Smith (1936, 1940), Kennard and Ectors (1938), Kennard (1939), and Richter and Hines (1938).

Among the anthropoid apes the chimpanzee has been the one most frequently studied. Results of stimulation of the frontal ocular cortex in this animal have been reported by Grünbaum and Sherrington (1901), Leyton (Grünbaum) and Sherrington (1917), Fulton and Bender (1938), and Dusser de Barenne, Garol, and McCulloch (1941a). The brain of the orang have been subjected to physiological investigation only five times, once by Beevor and Horsley (1890), once by Roaf and Sherrington (1906), once by C. and O. Vogt (1907), and twice by Leyton and Sherrington (1917). The gorilla has been studied even less than the orang, the only report in the literature on the results of electrical excitation of its cortex being that by Leyton and Sherrington (1917) who were privileged to study three animals.

In man, results of electrical stimulation of the frontal ocular region have been reported by Bechterew (1899, 1911), Foerster (1931, 1936), and Penfield and Boldrey (1937). The literature is replete with numerous clinical reports concerning the effect of lesions of this region or of its efferent fibers, and Foerster (1936) has reported alterations of function subsequent to excision of this region in man.

MONKEY

Position, Extent, and Topographical Relations

The position of the frontal region from which ocular responses have been elicited in monkeys is generally agreed upon by investigators, but reports as to the extent of this area on the surface of the brain have varied considerably. Ferrier (1874, 1875, 1876) definitely established the general position of the ocular responsive region in monkeys by showing that it was situated in the caudal part of the frontal gyri rostral to the precentral gyrus. He found the region to include a much smaller area than did later investigators, depicting it as constituting an almost circular field with the posterior part of the frontal sulcus (s. principalis, s. rectus) forming its lower or inferior boundary.

The more detailed investigations of Schäfer (1887) and of Horsley and Schafer (1888) resulted in considerable extension of the excitable area.
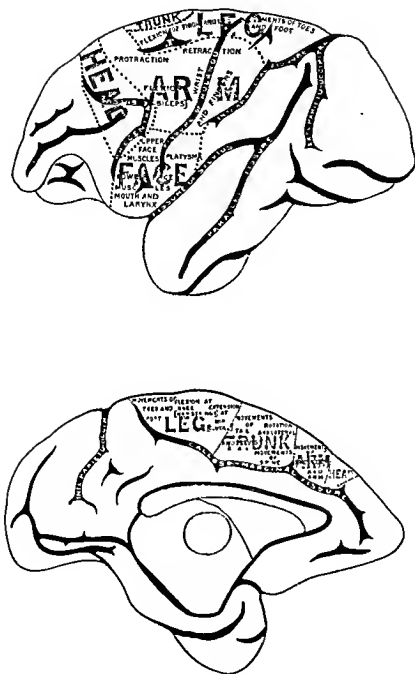
Fig. 106b.—The region yielding ocular movements, designated "Head" as determined by Horsley and Schäfer (1888) for the monkey (*Macaca sinica*)

Not only did they add to the ocular zone the cortex situated below the posterior one-third of the frontal sulcus, so that it now included almost all the cortex between the two arms of the arcuate sulcus (precentral sulcus on their diagram, fig. 106b), reaching almost to its lower end, but they extended the area superiorly over the edge of the hemisphere onto the medial surface as far as the sulcus cinguli (callosomarginalis) (fig. 106b) Their recognition of the extension of the eye zone, in addition to the precentral motor cortex, onto the medial surface of the hemisphere, and the extension of the eye field below the frontal sulcus, constituted an important contribution which has been verified by subsequent investigators On the other hand, their finding that a narrow strip of cortex situated just behind the lower ramus of the arcuate sulcus responded with movements of the head and eyes has not been confirmed by any other investigators except Mott and Schäfer (1890); if the response is not due to spread of stimulus it represents an unusual variation, for most investigators agree that the lower ramus of the arcuate sulcus usually defines the caudal limit of the frontal eye field.

The extent of the area as reported by Beevor and Horsley (1888) from their investigations on the lateral surface of the brain in *Macaca sinica* agrees in general with the findings of Horsley and Schäfer except in two instances: In the first place Beevor and Horsley, in agreement with most investigators, found that the area did not extend caudally beyond the lower ramus of the arcuate sulcus and, in the second place, in disagreement with subsequent investigators, Beevor and Horsley found that the responsive region extended inferiorly to the lower margin of the hemisphere (see p. 219).

Mott and Schäfer (1890), using large monkeys, including a variety of the genus Cercopithecus (Callithrix) and *Macaca mulatta*, and Levinsohn (1909), using the latter species, found the extent of the ocular responsive field to agree in general with that depicted by Horsley and Schäfer (1888), except that it did not extend caudally beyond the lower part of the arcuate sulcus.

Jolly and Simpson (1907) using species of Macacus and Cercopithecus limited the frontal region for ocular movement to the cortex enclosed between the s. frontalis and the superior ramus of the s. arcuatus, thus imposing a limitation not confirmed by other investigators.

The scattered foci which were found by C. and O. Vogt (1907) to yield movements of the eyes in a number of different species of monkeys lie within the region as depicted by Horsley and Schäfer. Their detailed studies on a number of individuals belonging to the genus Cercopithecus furnished more accurate data for delimiting the frontal ocular region, which in its superior part was found to extend farther rostrally than other

investigators had described it. Furthermore, they found that the eye field extended only a very short distance below the sulcus frontalis. As a result of additional studies on members of the genus Cercopithecus (species not given) the Vogts (1919) extended the ocular field still farther rostrally, and showed that the more rostral part possessed a threshold considerably higher than the caudal part (fig. 100, p. 266).

From the investigations reported on the two most common types of monkeys that have been used for experimental purposes, i.e., members of the genus Macaca and members of the genus Cercopithecus, it appears that the frontal cortex from which movements of the eyes can be elicited is situated rostral to the electrically responsive cortex of the precentral gyrus. No sulcus marks the caudal limit of this area in its superior part, but in many instances it reaches near or to the rostral end of the superior precentral sulcus. Below, its caudal boundary is usually found to be the lower ramus of the arcuate sulcus. The extent of the zone below the frontal sulcus varies from animal to animal, but in *Macaca mulatta* Smith (1936) never found it reaching to the end of the sulcus arcuatus (fig. 107). Its extension all the way to the lateral or inferior margin of the hemisphere as reported by Beevor and Horsley (1888) has not been confirmed by other investigators. Superiorly, the eye field extends over the edge of the hemisphere onto the medial surface as far as the sulcus cinguli (callosomarginalis). The rostral limit of the excitable zone is subject to variation, but superiorly in *Macaca mulatta* (Smith, 1936) it is often denoted by a shallow and almost vertical sulcus which is frequently covered by a vein draining into the superior longitudinal sinus. In Cercopithecus, C. and O. Vogt (1919) found that the excitable zone transcended this sulcus.

Caudal to the ocular zone on the mesial surface lies the electrically responsive field for the lower extremity; then from above and downward on the lateral surface the ocular zone is situated rostral to the regions for

Fig. 107.—Indicated subdivisions of the frontal eye field and the area yielding closure of the eyes in the monkey (*Macaca mulatta*) according to W. K. Smith (1936). Designations *a*, closure of eyes, *b* pupillary dilation, *c*, "awakening", *d*, conjugate deviation to opposite side, *e*, nystagmus to opposite side

the lower extremity, upper extremity, and face, in general as depicted by Horsley and Schäfer.

Responses to Electrical Excitation

Ferrier (1874) reported the production of ocular movements in monkeys (genus Macaca) from excitation of the posterior part of the superior and middle frontal gyri. Later (1875, 1876) in a more detailed account of his experiments he states: "The results of stimulation of these convolutions were always so uniform that the general result of experimentation in ten monkeys may be stated together. The results were:—Elevation of the eyebrows and the upper eyelids, turning of the eyes and head to the opposite side, and great dilatation of both pupils." Ferrier's discovery constituted the basis for all further investigations in this field and, although extension and modification of his findings, as applied to different members of the primate family, have been made by various investigators, his description of the results of excitation of this region in monkeys remains classical.

The fundamental physiological attributes of the frontal eye fields which Ferrier first described were later confirmed by Schäfer (1887) and Horsley and Schäfer (1888) without any important changes except in extent of the area. Beevor and Horsley (1888) stimulated the lateral surface of the hemisphere in *Macaca sinica* and, while agreeing with Horsley and Schäfer that the responsive area was much more extensive than Ferrier had reported, obtained results otherwise confirming and extending Ferrier's findings. Their work served to emphasize the fact that at times only a part of the complete complex movement may be obtained, and that rarely the eyes may turn slightly upward or slightly downward as they deviate laterally. They further emphasized the close association between turning of the head on the one hand and opening and deviation of the eyes on the other. Rarely did they observe the eyes turning to the opposite side without turning of the head. If the eyes happened to be in the position of conjugate deviation toward the same side, stimulation caused restoration of the direct position of the visual axes toward the front. In addition to these observations, Beevor and Horsley occasionally observed nystagmus, consisting of rapid jerking movements toward the opposite side, a finding that has been confirmed by later investigators. In most instances they noted no change in size of the pupils, but when a change did occur, dilatation always resulted. Their observations that opening of the contralateral eye may occur before that of the ipsilateral eye, and that movement of the eyeballs directly upward does not occur under ordinary conditions of cortical stimulation have been amply confirmed by other investigators.

Mott and Schäfer (1890) employed large monkeys of the genus *Cercopithecus* (*Callithrix* variety), the Bonnet monkey (*Macaca sinica*), and

a large rhesus (*Macaca mulatta*). They subdivided the ocular region according to the responses elicited. In large monkeys, but not in smaller ones, they concluded that it was possible to subdivide the excitable area on the lateral surface of the brain into three zones: a superior zone, situated above the superior ramus of the arcuate sulcus and extending to the mesial edge of the hemisphere, which produced movements of the head and eyes to the opposite side and downward; a middle zone, situated between the caudal half of the frontal sulcus and the superior ramus of the arcuate sulcus, which produced deviation of the head and eyes laterally; and an inferior zone, situated below the caudal half of the frontal sulcus, which produced deviation of the head and eyes to the opposite side and upwards. They observed that section of the corpus callosum had no effect on the responses and thereby established the principle that the integrity of the corpus callosum is not necessary for the production of bilateral movements from cortical excitation.

Mott and Schafer also studied the effects of bilateral faradization of points yielding the same response, i.e., lateral conjugate deviation of the head and eyes to the opposite side, and found that usually one side predominated over the other, so that the eyes deviated away from the dominant side. When, however, they carefully adjusted the strength of the stimulus so that each, when separately employed, produced about the same degree of response, bilateral simultaneous excitation caused the eyes to become fixed in a position as if the animal were looking ahead at some object with the visual axes apparently parallel or slightly convergent. If the eyes were in this primary position when the stimulus was applied, they remained motionless. Therefore, bilateral simultaneous excitation of the areas giving simple lateral conjugate deviation when excited unilaterally, was found to produce visual fixation, with no tendency for the eyes to deviate laterally. Excitation of the other zones was found to produce comparable results. Simultaneous bilateral excitation of the upper zone resulted in a simple downward inclination of the eyes without lateral deviation; bilateral excitation of the inferior zone caused a simple upward inclination without lateral deviation.

The subdivisions of the eye fields as advocated by Mott and Schäfer were not confirmed by the subsequent investigations of C. and O. Vogt (1907, 1919) or Levinsohn (1909). Furthermore, Levinsohn (1909) studied the responses of the eye fields in *Macaca mulatta* to bilateral stimulation and always obtained deviation of the eyes to one or the other side, and no movement of convergence was noted. In conformity with the results of other investigators, Levinsohn obtained movements of the head and eyes to the opposite side upon stimulation of the ocular responsive field. In most instances this deviation was not purely lateral, but contained an up or

down component. In the upper part of the responsive region, movement of the head usually began before movements of the eyes, and the threshold was definitely higher than in the lower part of the zone. Frequently the head and eye movements were accompanied by opening of the eyes Above the superior ramus of the arcuate sulcus movement of the head and of the opposite ear was sometimes obtained, occasionally accompanied by slight convergence of the eyes.

C. and O. Vogt (1907) found that the eye fields are separated from the electrically responsive region of the precentral gyrus by an inexcitable strip of cortex which they designated as the "inexcitable precentral field" (fig. 100, p. 266). Like previous investigators they obtained movements of the head and eyes to the opposite side, often with slight deviation upwards or downwards, and with or without opening of the eyes and dilatation of the pupils. Constriction of the pupils was rarely obtained. Movement of the ear, consisting of a drawing of the ear forward or backward, was observed in six instances, always on the contralateral side.

The Vogts also studied the problem of localization within the eye fields in order to determine whether or not it could be subdivided into portions yielding different responses Most of the excitable points yielding movements of the eyes to the contralateral side and upwards, with or without pupillary dilatation, were found to be located ventral to a continuation caudally of the sulcus frontalis. This region they designated as the *inferior ocular focus*. Foci yielding simple contralateral deviation of the eyes, with or without pupillary dilatation and opening of the eyes, were found to be situated mostly between the s. frontalis and the superior ramus of the s arcuatus. This region was designated as the *superior ocular focus* The cortex just above and adjacent to the superior ramus of the arcuate sulcus constituted another subdivision from which the complex response of contralateral deviation of the eyes accompanied by turning of the head in the same direction and opening of the eyes was elicited. In two instances eye opening was observed as the primary movement. This region was designated as the *zona complexa*. Above the zona complexa two subdivisions were made, one oral and one caudal The oral one contained the excitable points from which movements of the ear were elicited, either isolated or as part of a complex movement, and hence was designated as the ear zone. The caudal part contained most of the points from which opening of the eyes had been obtained, and hence was designated as the zone for eye opening.

A further attempt to subdivide the eye fields on the basis of their responses to electrical stimulation was made by Smith (1936) on *Macaca mulatta*. In no instance were clear-cut physiological subdivisions yielding

only one type of response found, but it was disclosed that certain types of responses were more easily and more frequently elicited from certain portions than others. While it was realized that these criteria for subdividing a cortical field were far from being adequate, yet it was hoped that they might suggest the possibility of, and serve as a basis for, such an analysis of the eye fields in the anthropoid apes and eventually in man. On the basis of the criteria just given, it appeared that the portion of the eye fields on the lateral surface of the hemispheres could be divided into four zones (fig. 107).

Stimulation of an area which is situated rostral to the arc of the s. arcuatus and which surrounds the caudal end of the s. frontalis resulted in the production of nystagmus of both eyes, the fast component being directed toward the contralateral side. If the eyes were closed, opening of the eyes occurred simultaneously with the production of the nystagmus. Conjugate deviation of the eyes not only occurred in the initial part of the nystagmus, but was elicited without the accompanying nystagmus from an area situated medial to the "nystagmus" field. It was always contralateral and frequently was found associated with turning of the head in the same direction and opening of the eyes, if the eyes had been closed before the stimulus was applied.

An interesting complex group of movements, which together simulate an awakening, was designated as the "awakening response." This was elicited from the region around the medial end of the arcuate sulcus. The animal, though anesthetized, upon application of the stimulus appeared to awaken and to become aware of his surroundings. The eyes, while opening, slowly deviated to the contralateral side, the pupils dilated (even in strong light), and blinking occurred. Struggling movements frequently ensued.

Pupillary dilatation was most easily elicited from an area adjacent to the medial border of the hemisphere. In normal animals it appeared to be always a bilateral phenomenon, and usually no significant difference could be detected as regards the degree of dilatation on the two sides.

From the evidence presented by the various investigators it would appear that in the monkey a variety of responses can be obtained from excitation of the frontal ocular responsive cortex. The most complex movement is one of opening of the eyes accompanied by turning of the head and eyes toward the opposite side and dilatation of the pupils. This response is most easily elicited from the upper part of the eye field, while nystagmus with the eyes in the deviated position is most easily elicited from the lower part, around and below the sulcus frontalis. The response from the eye field, like that from other cortical regions, may vary, depending on such factors as depth of anesthesia, strength of stimulus, condition of cortex,

and general condition of the animal. Movement of the eyes may occur without movement of the head, or more rarely the reverse is seen. A brief application of the stimulus may produce only a part of the response, e.g., opening of the eyes. The eyes may turn slightly upward or downward as they deviate laterally. Movements of the eyes may occur without pupillary changes, and less frequently the reverse may be observed. Movement of the head or eyes may occur without opening of the eyes, particularly when the animal is in deep anesthesia or in a state of exhaustion. Under light anesthesia nystagmus in which the fast component is directed toward the contralateral side can be regularly elicited, but this response is altered to one of simple deviation when the anesthesia is deepened (Smith, 1936).

The fact that tonic or clonic movements, purely lateral or combined with an upward or downward component, are the only ones regularly elicited from excitation of the frontal ocular field, suggested to investigators the possibility that other movements might be obtained upon cortical excitation if the dominant lateral movement was excluded by rendering inactive the muscles producing it. Russell (1894), acting on the suggestion of Hughlings Jackson, divided the external rectus muscle of the contralateral eye and the internal rectus of the ipsilateral eye, on the basis of the hemisphere stimulated, in the monkey (*Macaca sinica*) and then subjected the frontal eye region to electrical stimulation. In other monkeys, only the external rectus muscle of the opposite eye was divided, and in another series both the medial and lateral recti of the opposite eye only. Unfortunately the results obtained upon electrical stimulation of the ocular region in these experiments are scarcely more than enumerated, and hence it is not possible to analyze them in terms of the peripheral lesion. However, under the various circumstances as outlined, in contrast to the responses obtained when the eye muscles were intact, stimulation of the cortex along the superior ramus of the arcuate sulcus produced direct upward or downward associated movements of both eyes, while stimulation just at the caudal end of the s. frontalis sometimes produced convergence. Rarely the eyes moved toward the side stimulated. Even the great lack of detail which characterizes this report cannot detract from its importance, for the results show that movements of the eyes other than that of lateral conjugate deviation are represented in the cerebral cortex, but that in ordinary stimulation experiments the cortical mechanisms producing downward or upward associated movements of the eyes are unable to manifest themselves because of the dominance of the mechanism for lateral movement.

The law of reciprocal innervation of antagonistic muscles as propounded by Sherrington has received additional support from the response

of the eye muscles to cortical stimulation. In experiments on monkeys, Sherrington (1893) showed that if all the muscles to one eye except the external rectus are paralyzed by section of the oculomotor and trochlear nerves, and if, subsequently, a point in the ipsilateral hemisphere previously yielding conjugate deviation of the eyes to the opposite side is stimulated, both eyes still move in the same direction, thus demonstrating an inhibition of tonus in the left external rectus by cortical excitation. This tonic inhibition was further substantiated by the finding that, after section of the oculomotor and trochlear nerves going to both eyes, simultaneous bilateral excitation of the cortical region normally yielding lateral deviation when excited separately, produced convergence of the eyes even though a divergent strabismus had previously been caused by section of the nerves. From further experiments, he showed that cortical excitation could produce inhibition of the process of active contraction in the eye muscles, as well as inhibition of tonus.

Evidence that excitation of the frontal eye region can produce inhibition of activity in muscles other than those which it can also excite is furnished by the investigations of C. and O. Vogt (1919) (fig. 100, p. 266). They found that excitation of the cortex situated anterior to the arcuate sulcus and limited above by extending the s. frontalis caudally (Vogt's area 8β) would not only extinguish a response that was being elicited by excitation of the region for facial movements but would prevent the reappearance of the response when stimulation of the facial cortex was continued. A similar inhibitory influence on the precentral area responding with movements of the arm and fingers was found upon weak excitation of the cortex (Vogt's area 8α) situated within the bend of the s. arcuatus and above the level of the s. frontalis. Below these regions in Vogt's area 8γ excitation caused an inhibition of masticatory movements elicited from excitation of the cortex just caudal to the lower end of the s. arcuatus (Vogt's area 6bα). Although the Vogts listed the apparent inhibitory influence of 8α and 8β as questionable, their findings heralded the discovery by Dusser de Barenne, Garol, and McCulloch (1941a, b) that strychninization or electrical stimulation of a strip of cortex in the frontal lobe including the region yielding lateral conjugate deviation of the eyes not only caused a suppression of the electrical activity of the precentral gyrus, but also rendered the precentral gyrus temporarily unresponsive to electrical stimulation (see Chapter VIII).

Graham Brown (1922) studied the effect of stimulation of the frontal eye fields in the monkey on what he designated as the "orientation of the optical axes reflex," the adequate stimulus for which he concluded was labyrinthine, for it could be elicited after removal of the brain rostral to

the superior colliculus. This reflex he defined as that which keeps the optical axes fixed in relation to external space, so that when the head is moved in one direction the eyeballs move in a conjugate manner, equally and in the opposite direction. It was found to be present in monkeys under light anesthesia, but disappeared when the anesthesia was deepened Stimulation of the upper part of the frontal ocular area was found to "awaken" the reflex so that it manifested itself again. If the eyeballs were already centered they did not move in the head, but if they were directed to one or to the other side just before the time of stimulation, they then moved to the center position and remained fixed in their sockets, even though the head deviated toward the opposite side. If the head was restrained, excitation produced lateral conjugate movements of the eyes to the opposite side. From this he inferred that the cortical response was such as to move the eyeballs in the same direction as the head, but of equal and opposite degree to that evoked by the orientation reflex. However, another explanation would seem to suffice, namely, that stimulation of the upper part of the frontal eye field suppressed the orientation reflex, perhaps by an inhibitory effect on the vestibular mechanism.

The fact that the frontal ocular cortex is able to superimpose its activity upon that of the vestibular apparatus without abolishing the responses of the latter, is shown by the experiments of Bárány and C. and O. Vogt (1923). These investigators, working with monkeys (*Macaca mulatta*), found that during a contralateral nystagmus (quick component toward the right) produced by syringing the left ear with cold water, stimulation of area 8 or 6aβ (of the Vogts) of the left hemisphere resulted in deviation of both eyes in the same direction, the nystagmus either remaining unchanged or increasing in rate and decreasing in amplitude. By recording the activity in individual muscles of the ipsilateral eye they observed that nystagmus of this eye in the deviated position was produced by the action of the internal rectus only, the external rectus remaining completely relaxed.

Closure of the eyes in monkeys is not obtained from that part of the frontal region from which movements of the eyeballs are elicited, but results from excitation of the facial region of the precentral gyrus situated just caudal and inferior to the arc of the arcuate sulcus (fig. 107). The separation of the two responses in the cerebral cortex should occasion no surprise. for the two movements are brought about by quite different functional groups of muscles. the extrinsic eye muscles and the orbicularis oculi, the former innervated by the oculomotor, trochlear, and abducens nerves, the latter by the facial nerve. The discovery of the area for eye-closure in the monkey (*Macaca innus*) by Hitzig (1876) was followed by

reports from a number of investigators who found the response elicitable from the upper part of the facial region, somewhat inferior to the point designated by Hitzig in the drawing accompanying his report. In electrical stimulation of this region the current strength can be made so weak as to limit the observable response to the opposite side only, but with a stronger stimulus complete closure of the contralateral eye and partial closure of the ipsilateral eye results. Further increase in the stimulus strength results in closure of both eyes, the response being most pronounced on the contralateral side. The contralateral cortical control of this movement therefore seems greater than the ipsilateral.

Results of Unilateral and Bilateral Ablations

About a decade after the discovery of the frontal eye fields in the brain of the monkey, Ferrier and Yeo (1884) reported the results of destruction by cauterization of various regions of the cortex. Four of their experiments are relevant to the subject under discussion, since the lesion, as shown grossly in photographs of the brain after its removal postmortem, involved the frontal eye fields. While the methods were crude as compared to modern ones and occasionally accompanied by infection, their results laid the foundation for the study of the physiological deficit in ocular movements resulting from ablation of this region both unilaterally and bilaterally. These experiments demonstrated the fact that unilateral ablations which included the frontal eye fields result in an immediate deviation of the head and eyes toward the side of the lesion when the animal is at rest and is accompanied by impairment of ability to turn the head and eyes toward the opposite side. The alterations of function were found to be temporary, and within a few days no obvious abnormality was present.

After simultaneous bilateral destruction of the eye fields the head and eyes did not deviate to the right or left. On the contrary, they appeared more or less fixed in the middle axis and turning of the head and eyes did not occur either to the right or to the left. When the animal turned it moved the head and body as a whole, thus executing a wide circular movement which these investigators considered to be due to the impaired lateral mobility of the head and eyes. This alteration in function, like that occurring after unilateral ablations, was only of temporary duration, in some instances disappearing within two or three days after operation. It was noted that the activity of the animal showed alternating periods of apathy and of apparent purposeless restlessness. During the latter it was in an almost constant state of activity, "running about incessantly and fumbling among the straw at the bottom of the cage." This increased activity persisted, and in one animal was present until it died eleven days later.

One of the most remarkable findings in the field of the physiology of nervous system in primates, and one for which a satisfactory explanation still is lacking, was reported by Bianchi (1895, 1922) following ablations in the frontal lobe involving the ocular responsive region. In baboons (*Cynocephalus poicarus*) and monkeys (probably Cercocebus), following unilateral extirpation of this area in the cortex, which in some instances included approximately the caudal half of the middle and inferior frontal gyri, Bianchi observed that the animals apparently were blind in the halves of the visual fields opposite to the lesion. In the somatic motor realm also, profound alterations were effected. The animals exhibited persistent restlessness and frequent circling movements toward the opposite side. Most of the somatic motor activity was performed in a stereotyped manner, listlessly, aimlessly, and automatically. Furthermore, the animals appeared stupid and were indifferent to objects in which they formerly displayed a lively interest. When threatened they made no attempt to defend themselves, but showed signs of great fear. When given a piece of sugar and a piece of chalk, the animals chewed and swallowed both without discrimination. Gradual improvement occurred, but several weeks after the operation the alterations in function were still present though exhibited to a less degree. Ablation of the corresponding area on the opposite side now not only precipitated the alterations in their full intensity, but they were of a more enduring nature.

Circling movements in monkeys (*Macaca mulatta*) subsequent to lesions of the frontal part of the brain have recently been studied by Kennard and Ectors (1938) and Kennard (1939). From their experiments they concluded that destruction of a relatively small area of cortex situated within the bend of the arcuate sulcus, i.e., an area corresponding to Brodmann's area 8 as shown on his map of the Cercopithecus (fig. 95, p. 249), was sufficient to produce deviation of the head and eyes to the same side. In addition they found the circling movements, the restless, aimless and stereotyped activity, and the visual defect which Bianchi had reported following more extensive lesions. Extirpation of the same region on the other side of the brain resulted in reversal of both the circling movement and the deviation of the head and eyes. Bilateral simultaneous ablation of the region produced the same results as extirpation of all the prefrontal cortex including this area. After recovery from the operation the animals remained motionless with a fixed gaze directed straight ahead. Movements of the eyes rarely occurred and blinking appeared infrequent. Although the animals appeared to be blind, if a moving object was brought within the visual fields the eyes followed it, but at the end returned to the central position, and rage reactions sometimes resulted from visual stimuli. The animals were observed to walk into objects, striking their heads against

the cage and to reach for and grasp anything offered them, after which they appeared not to know what to do with it. These symptoms gradually abated and after a few weeks the animals appeared nearly normal except for a "wooden" expression and fixed gaze. Restless and purposeless "forced" activity of a stereotyped character and circling movements, sometimes to one side and sometimes to the other developed as the first class of symptoms receded. Ablation of the cortex rostral and medial to this region failed to produce either the visual defect, the alterations in motor activity, or the "intellectual" deficit While Kennard and Ectors (1938) conclude from their investigations that the "intellectual" deficit can be accounted for by the alterations in visual and motor function, later studies by Kennard (1939) led to the conclusion that the altered behavior exhibited by these monkeys was due to a "disturbance of the more complex integrative process of the frontal lobe."

Richter and Hines (1938) investigated the increase in spontaneous activity in monkeys (*Macaca mulatta*) produced by lesions of the frontal part of the brain and arrived at conclusions at variance with those of Kennard and Ectors Richter and Hines found that increased spontaneous activity occurred after lesions of the prefrontal regions completely sparing area 8 and that no increase in activity occurred after either unilateral or bilateral removal of this area alone In fact, after bilateral removal of area 8 activity decreased slightly Circling movements were not present except when the animals were confined to small cages Hines and Richter point out that the small size of area 8, together with the variation in extent from animal to animal, makes it difficult to remove this region without damage to other areas. Kennard and Ectors found that lesions restricted to the surface of the cortex failed to produce the alterations which they described. These were only obtained when the lesion was carried into the depths of the sulcus arcuatus The deep and undermining character of their lesions lends credence to the probability that portions of the cortex other than area 8 were involved either directly or through interruption of projection fibers due to the encroachment of the lesion on the white matter.

Clark and Lashley (1947) found that, in order to produce an homonymous hemianopia in monkeys, the cortical ablation must include more cortex than that within the limbs of the arcuate sulcus. The visual field defect was not always accompanied by circling movements or by deviation of the head and eyes Furthermore, the hemianopia could be produced by a transverse lesion of the subcortical white substance which included severance of the superior longitudinal fasciculus. On the basis of these studies they came to the conclusion that, "the visual defect represents a traumatic disorganization of re-entry circuits producing interaction between the frontal and occipital regions."

THE ANTHROPOID APES

While the general position of the frontal eye fields in the anthropoid apes would appear to be constant, the extent of this region on the surface of the brain and its topographical relations to the various sulci are subject to considerably more variation than is the case in the lower primates. Not only is there dissimilarity of convolutional pattern in the chimpanzee, orang, and gorilla, but there is considerable variation from animal to animal in the same species and even in different hemispheres of the same animal. This dissimilarity of convolutional pattern, as Leyton and Sherrington (1917) pointed out, make it well-nigh impossible to decide exactly what point on one cerebral hemisphere is identical with a given point on another hemisphere of the same or of a different animal. The situation is further complicated by the fact that the anthropoid apes form no exception to the general rule that not only is there a considerable amount of electrically responsive cortex buried in the depths of the sulci (Leyton and Sherrington, 1917; Smith, 1940), but the depth varies from animal to animal and from hemisphere to hemisphere in the same animal.

Our knowledge concerning the ocular responsive cortex in the great apes consists exclusively of the results of excitation, except for the brief note on the results of unilateral extirpation of the eye fields in a chimpanzee by Fulton and Bender (1938).
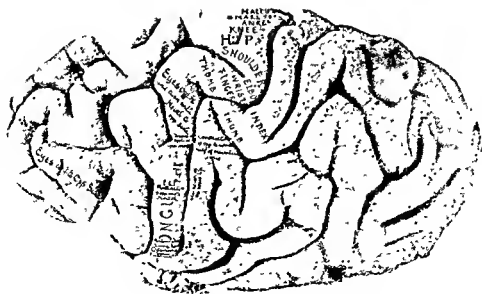
Fig. 108 —The frontal eye fields in the orang as determined by Beevor and Horsley (1890)

Orang

The first experiment on the electrical excitation of the brain in anthropoid apes was reported by Beevor and Horsley in 1890 These investigators stimulated the lateral surface of the cerebral hemisphere in a young orang of an estimated age of two and one-half years. Two anatomically discrete areas producing movements of the eyes were found. One was situated rostral to the precentral sulcus and for the most part superior to the caudal half of the inferior frontal sulcus, the other was situated in the precentral gyrus, being bordered superiorly by the area for the hand and inferiorly by that for the face (fig 108). Corresponding to their anatomical discreteness, these areas were found to yield ocular responses differing in type. Stimulation of the precentral area produced a complex movement consisting of opening of the eyes accompanied by turning of the head and eyes toward the contralateral side, while excitation of the more rostral region yielded only conjugate lateral deviation of the eyes to the opposite side.
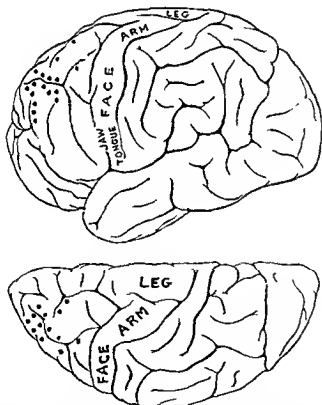
Fig 109—The motorically responsive cortex as found in the orang by Leyton and Sherrington (1917). The dots represent ocular responsive foci (Redrawn after Leyton and Sherrington).

The two responsive points described by Roaf and Sherrington (1906) and the single point reported by C. and O. Vogt (1907) lay within or near the more rostral area described by Beevor and Horsley, and all responded similarly to electrical stimulation.

Leyton and Sherrington (1917) stimulated the cortex in two orangs and found responsive points in the region of the more rostral area of Beevor and Horsley, but scattered over a larger extent. In addition to excitable foci yielding conjugate lateral deviation of eyes to the opposite side, others were found yielding deviation of the head and eyes accompanied by opening of the eyes (fig. 109).

Chimpanzee

The chimpanzee has been the most frequently investigated of all the anthropoid apes. Electrical stimulation of the cerebral cortex in this animal was first reported by Grünbaum and Sherrington (1901), who depicted a rather extensive area from which conjugate deviation of the eyeballs could be elicited (fig. 110). The ocular area was separated from the electrically responsive cortex of the precentral gyrus by an inexcitable zone. Sixteen years later the same investigators (Leyton and Sherrington, 1917) gave a
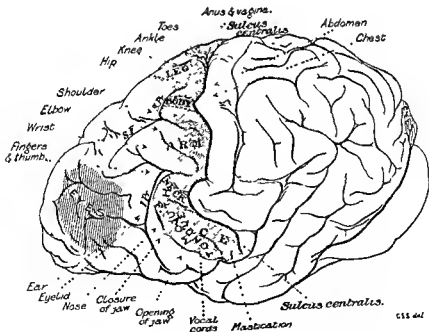
Fig. 110—The frontal eye field in the chimpanzee according to Grünbaum and Sherrington (1903). Excitable foci within or near this region were reported by Leyton and Sherrington (1917), but the limits of the field were not defined

more detailed report of the results obtained from stimulation of the cortex in twenty-two chimpanzees. A number of excitable points were found scattered both above and below what appears to be the caudal part of the horizontal (superior) ramus of the s. praecentralis superior; they are, therefore, situated for the most part within what is generally regarded as the middle frontal gyrus. The more superior of these points yielded conjugate deviation of the eyes to the opposite side combined with pupillary dilatation; the more inferior of the points yielded a similar movement of conjugate deviation combined with opening of the eyes. Occasionally the eye movements were accompanied by turning of the head in the same direction. Convergence was rarely observed.

In a chimpanzee in which the right oculomotor nerve had been severed, Fulton and Bender (1938) found scattered points yielding ocular responses in what appears to be the same general region as that depicted by Leyton and Sherrington. From stimulation of the left ocular responsive region they obtained conjugate deviation of the eyes towards the opposite side, accompanied by opening of the eyes. At times either one or the other movement was elicited alone. Stimulation of the right cortex elicited conjugate deviation towards the left, the right eye with its internal rectus paralyzed by previous section of the oculomotor nerve, deviating as far as the middle position thus apparently confirming Sherrington's (1893) finding that excitation of the ocular cortex could inhibit tonus in the eye muscles that are antagonists during eyeball movement. Furthermore, they noted the long latency of the responses as much as 6 or 8 seconds, and observed that after interruption of repeated stimulation which had caused deviation to the opposite side, the eyes would often deviate in the opposite direction. This secondary deviation was interpreted as due to relaxation of the fatigued muscles.

Dusser de Barenne, Garol and McCulloch (1941a) depicted the eye field as a band of cortex, widest in its superior part and, in general, extending from near the medial to near the lower margin of the hemisphere, although variations were found. They obtained ipsilateral as well as contralateral conjugate deviation of the eyeballs and from the superior portion of the field pupillary dilatation and lacrimation. They concluded that in general the frontal ocular responsive cortex coincided with their suppressor band I (see Chapter VIII), for in addition to ocular responses, its excitation was found to have a pronounced inhibitory influence on the more caudally situated cortex, as shown by suppression of response to electrical excitation and holding in abeyance after-discharge. As a result of their work, it would appear likely that the mexcitable cortex which Leyton and Sherrington (1917) and others found present between the precentral field

and the eye fields came about as a result of suppression of response, due either to previous excitation of the frontal eye fields, or to previous excitation of the more caudal suppressor band. (See fig. 82, p. 218.)

The results of unilateral ablation of the ocular responsive region in the chimpanzee have been briefly described by Fulton and Bender (1938) In the chimpanzee referred to above, in which the right oculomotor nerve had been sectioned intracranially, the left frontal ocular region was extirpated. After recovery from the anesthetic, the left eye, with its peripheral innervation intact, was found to be deviated towards the left, and its movement past the midline towards the right was definitely restricted. There was deviation of the head towards the left, and when the animal walked it always turned in that direction, thus executing circling movements similar to those occurring in monkeys. No visual defect was found, the animal reacting to test objects presented in the right as well as in the left visual field. Six hours after operation, deviation of the head had almost disappeared Circling movements persisted and were present eighteen hours after the operation, when the last observation was made on the non-anesthetized animal. From this single experiment it appears that unilateral extirpation of the ocular responsive cortex in the chimpanzee results in defects of ocular movement and circling movements similar to those reported for the monkey. The explanation of the absence of visual defect and the presence or absence of any intellectual deficit must await further investigation.

Gorilla

The only account of electrical excitation of the cerebral cortex in the gorilla is that given by Leyton and Sherrington (1917). These investigators studied the electrically responsive cortex in three animals As in the chimpanzee, they found the eye fields to be situated in the caudal part of the inferior and middle frontal gyri, rostral to the region from which the movements of the hand and face could be elicited. Excitation produced either the complex movement of opening of the eyes accompanied by turning of the head and eyes to the opposite side, or one or more parts of this complex response. No indication of the limits of the responsive region is shown.

MAN

Results of Excitation

The knowledge which we possess concerning this region of the cortex in man has been derived mainly from reports by Foerster (1931, 1936) and Penfield and Boldrey (1937), but to Bechterew (1899b) must be given credit for having first shown that electrical stimulation in the region of

the caudal part of the middle frontal gyrus in man resulted in conjugate deviation of the eyes and turning of the head to the opposite side.

Foerster (1931, 1936) found that excitation of the region comprising the foot of the middle frontal gyrus, just rostral to that part of the precentral gyrus from which he obtained movements of index finger, thumb, and neck muscles resulted in movements of both eyes toward the contralateral side (fig. 111). The eye field was identified cytoarchitecturally as corresponding to area 8αβδ of the Vogts. Excitation with the galvanic current produced a short quick twitch; excitation with faradic a conjugate deviation of the eyes during application of the stimulus, in each instance unaccompanied by turning of the head. Frequently the lateral deviation was associated with a slight upward movement, rarely with a downward component. Purely upward or purely downward movements of the eyes without lateral deviation were very rarely seen and then only as isolated movement of one eyeball. No definite change in size of pupil could be ascertained. Occasionally it was noted that upon application of the stimulus the eyes deviated slightly toward the stimulated side and then quickly reversing their direction moved toward the opposite side. No sensation was aroused by excitation of this field. In harmony with the findings of various investigators from studies on monkeys and anthropoid apes, the threshold for this area was found to be decidedly higher than that for the precentral region, and galvanic excitation frequently was ineffective. The response of this region was not altered by excision of area 6αβ (of the Vogts and Foerster; area 6 in this monograph) or by removal of the entire precentral convolution.

As had been previously demonstrated by the Vogts (1919) in the monkey, Foerster found that area 9 in man responded with turning of the eyes to the opposite side only when a strong stimulus was used, the threshold for area 9 being higher than that for area 8. After extirpation of area 8αβδ (of the Vogts), the responsiveness of area 9 was abolished.

Epileptic attacks produced by excitation of the ocular area were found to begin with clonic movements of the eyes toward the opposite side, the clonic movements soon changing into a tonic deviation in the same direction. No visual aura was associated with the attack.

Ordinarily area 6aα (of the Vogts and Foerster; area 4a in this monograph) responded to faradic stimulation with isolated movements of various parts of the extremities just as did area 4. But, after excision of area 4 strong faradic stimulation of area 6aα produced a complex movement in which the head, eyes, and trunk turned toward the opposite side with complex synergic movements of flexion and extension of the contralateral limbs. These responses were abolished by undercutting the cortex or by coagulating it.
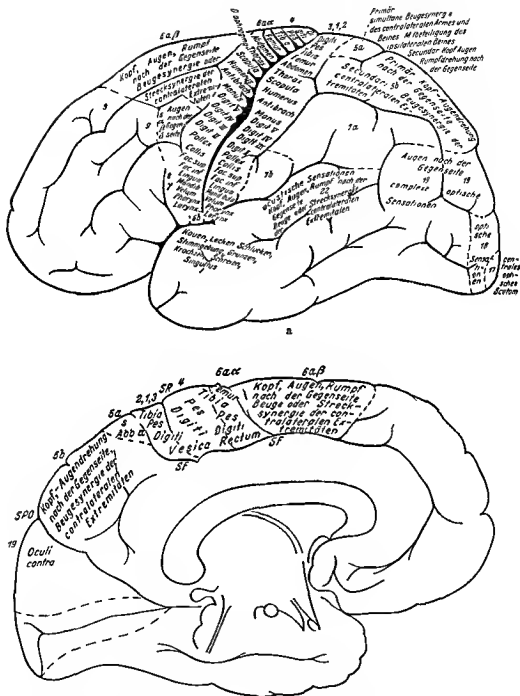
Fig. 111.—Foerster's (1936) map of the response cortex in man. In addition to the indicated ocular response cortex, eye movements were obtained from cortex stimulated more rostrally if a stronger stimulus was used

Area 6aβ (of the Vogts; area 6 in this monograph) required strong faradic stimulation to give a response and under general narcosis it was found completely inexcitable. The response consisted of rotation of the head and eyes towards the opposite side. The response of 6aβ was elicitable after destruction of area 4 or after ablation of the precentral convolution or its efferent connections. If, however, the efferent fibers from 6aβ were interrupted in the corona radiata the response to electrical excitation no longer occurred.

Penfield and Boldrey (1937), employing a thyratron stimulator with a frequency of 55 to 65 per second (characteristics of wave and intensity not given), obtained eye movements from points scattered over a wider region of the frontal cortex than was reported by Foerster. Responsive foci were found in the caudal part of the superior, middle, and inferior frontal gyri, as well as in the precentral gyrus (fig. 112). As indicated in their drawing, these foci were found in regions corresponding to areas 6aα, 6aβ, 8, and 9 of the Vogts. The only response elicited consisted of lateral conjugate deviation of eyes to the opposite side, often with an upward, never with a downward component. Turning of the head to the opposite side did not accompany the eye movements except in a few instances, and then it was obtained not from area 6aβ as Foerster reported but from stimulation of the precentral face area. In addition to motor responses, in two cases the
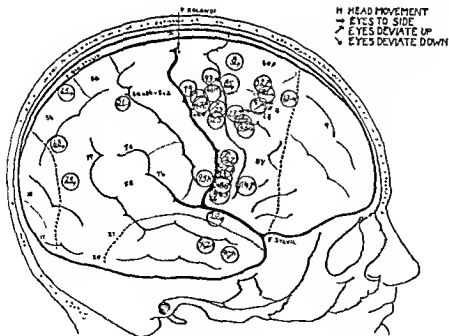
Fig. 112—Ocular responsive cortex in man as reported by Penfield and Boldrey (1937).

subjects experienced a sensation, usually one of movement, in the eyes from stimulation of the caudal part of the middle frontal and adjacent part of the precentral gyri, although no movement of the eyes was discernible.

Effect of Lesions

The frequent complexity of lesions occurring in the brain of man, the lack of definite anatomical limitation in most instances, and the possibility of signs and symptoms occurring as a result of indirect involvement of remote regions, make for cautiousness and conservatism in attempting to assess the direct effect of any intracranial lesion. Furthermore, slowly progressive lesions, such as tumors, involving certain regions of the cortex may produce no discernible alterations in function because of the existence of compensatory mechanisms which come into operation simultaneously with the localized destruction of the nerve elements. Thus it happens that, in most instances, acute lesions producing destruction of a cortical region are more likely than slowly progressive ones to cause signs and symptoms. This is particularly true of the frontal eye fields, for experiments on animals demonstrate that the alterations occurring after unilateral ablation disappear to a great extent within a short time, and even those occurring after bilateral ablation are largely compensated for after the lapse of a slightly greater length of time. Nevertheless, the available evidence from clinical studies on man seems to indicate clearly that acute lesions destroying either the cortex in the vicinity of the caudal part of the middle frontal gyrus, or as more frequently occurs, interrupting the efferent fibers from this region as they pass through the internal capsule, produce alterations in function, as regards ocular movements, in a manner comparable to that seen in monkeys after ablation of the corresponding cortical region.

It is a well-established fact, emphasized by Prevost (1868), that many cases of hemiplegia resulting from lesions in the internal capsule show a deviation of the head and eyes toward the side of the lesion early in the affection. Roux (1899) concluded that those cases associated with an homonymous hemianopia were due to a lesion involving either the visual cortex of the occipital lobe or the visual pathway, while those cases showing no defect of the visual fields resulted from a lesion either in the region of the caudal part of the middle frontal gyrus, or from interruption of efferent fibers from this area as they passed through the internal capsule. In the former instance voluntary movements of the eyeballs remained, in the latter voluntary movements were lost, but reflex movements resulting from visual impulses were present, so that the eyes followed moving

objects. The correctness of Roux's conclusions has been amply confirmed by subsequent clinical and experimental studies.

The striking features of frontal oculomotor dysfunction in man due to unilateral destruction of the frontal eye field are described in detail by Gordon Holmes (1938). Although the paresis resulting in these cases is variable, in a typical one the patient is unable to move the eyes when ordered to do so, although an attempt is obviously made, sometimes accompanied by expressions of great distress. If however, he is asked to look at an object and then the object is slowly moved either toward the opposite side or upwards or downwards, the eyes follow it and the movements may execute the full range normally attained. However, if the object is rapidly moved, the eyes follow it for only a short distance and then return to their position of deviation, or if while the eyes are following a slowly moving object it is suddenly moved rapidly or jerkily so that fixation is interrupted, the eyes cease to follow and then return to the deviated position. Furthermore there is an absence of optic nystagmus which is normally elicited when a slowly revolving drum, on which are placed vertical lines, is looked at. Convergence on a near object may also be defective, but when slowly aproached from a distance convergence seems normally executed. Although movements of the eyes cannot be voluntarily brought about, if two points on a sheet of paper are connected by a line, or if a series of dots are placed between them the eyes may follow along the line or dots until they reach the other side. Having reached the end of the line they may remain fixed in that position until the impulses originating in the fovea centralis are extinguished either by blotting out the object fixed upon, e.g., by closing the eyes or by moving the head, or by moving the finger along the line in the reverse direction. By this latter method reading may be accomplished, for the finger can be used to lead the eyes back and forth across the page. Movements of the eyes can also be brought about by active or passive movement of the head during which the eyes move through an equal angle, but in the opposite direction. That this compensatory deviation is not due to impulses of labyrinthine origin, but to the influence of foveal impulses, Holmes thinks is shown by the fact that the eyes remain in the deviated position after head movement ceases, and that the compensatory ocular movement does not occur if the eyes are closed. Unilateral destruction of the frontal ocular region, therefore, results in a disorder of ocular movement. Under such circumstances eye movements cannot be performed voluntarily, but under the influence of foveal impulses the movements may encompass the normal range. It therefore seems that the frontal ocular region not only provides for volun-

tary movements of the eyes, but it is also concerned with influencing the visual fixation reflex, chiefly in the form of releasing the eyes from its control, thus permitting them to become fixed on other objects. Bilateral lesions such as occur in pseudobulbar palsy render voluntary ocular movements difficult or impossible, but reflex movements dependent upon visual impulses appear to be well performed.

That alterations in ocular movement are not reported in every case of lesion of the internal capsule may be due to the fact that in some capsular lesions, fibers concerned with ocular movement may not be involved, and in others the alteration in function may be of so short duration as to escape observation, while in the case of slowly progressive involvement, either of the cortex or of the internal capsule, compensatory adjustments may occur simultaneously with the progress of the lesion, so that no physiological deficit is discernible.

The less frequent occurrence of deviation towards the side opposite the lesion may be explained by the presence of an irritative lesion having an excitatory effect on the cortical eye field or its efferent fibers, for the evidence from experiments on animals seems to demonstrate conclusively that destruction of the frontal eye field never results in deviation of the eyes towards the contralateral side.

To the knowledge which we possess concerning alterations in eye movements subsequent to lesions of the frontal part of the brain which involve the frontal eye field or its efferent fibers, Foerster (1936) has added findings concerning the effects of surgical removal of the ocular responsive cortex in man. According to Foerster's investigations, alterations of eye movement do not occur as a result of removal of any portion of the frontal lobe except the caudal part of the middle frontal gyrus. This region he designates as area $S_a\beta\beta$ corresponding to the Vogts' chart. Following excision of this region in man, Foerster found that the eyes were not deviated, but maintained the usual position toward the front. There existed an inability of the patient to turn the eyes toward the opposite side upon command, together with a lack of spontaneous glancing toward the side opposite the lesion. Eye movements produced by moving an object upon which the patient had fixated, either executed the full range of movement or, in some instances, showed definitely limited excursions.

The findings for man, therefore, are only partially in agreement with those described by some observers as occurring after destruction of the frontal ocular field in monkeys. The available evidence indicates that man does not exhibit the "forced circling" movements, the "intellectual deficit," the change in personality, nor the visual defect which have been described after lesions of the frontal eye field in monkeys.

CYTOARCHITECTURAL SUBDIVISIONS

The interest aroused by cytoarchitectural studies of the cerebral cortex, especially those of Campbell (1905) and Brodmann (1909), resulted in new attempts at analyzing its functions. Up to that time most investigators had reported the results of excitation and extirpation in terms of anatomical regions of the brain, or of extirpation in terms of the area yielding a particular response upon excitation, and it is on this basis that most of the reports dealing with the frontal eye fields have been made. Following the work of Campbell and Brodmann, interest began to be centered in attempting to correlate the results of excitation and extirpation of various cytoarchitectural regions.

The work of the Vogts (1907, 1919, 1926) on electrical stimulation of the cerebral cortex in monkeys (members of the genus Cercopithecus) culminated in considerable knowledge regarding the possible functional role in these animals of the various cytoarchitectural areas described by Brodmann (1909) (figs. 95, p. 249, and 100, p. 266). Their experiments showed that movements of the eyes could be elicited from areas which they designated $6a\beta$, $8a\beta\delta\gamma$, $9c$ and $9d$, and the rostral part of area 10. From area $6a\beta$ (comparable to area 6 in this monograph) eye movements occurred as part of a complex movement including deviation of the eyes and turning of the head and curving of the trunk toward the opposite side, accompanied by movements of the opposite ear. If a stronger stimulus was used, this would be followed by synergistic movements of the opposite arm and leg. They designated this area as the frontal field for adversive movements and found that with stronger stimulation similar responses could be elicited from $9a$ and $9b$. The upper portion of area 8, designated by the Vogts as $8a\beta\delta$, was found to be the most easily excitable field for conjugate lateral deviation of the eyes. Rostral to this area, $9c$ and $9d$ gave a similar response, but a stronger stimulus was necessary. Still farther forward in the caudal part of area 10, just below the sulcus frontalis, conjugate ocular deviation could be elicited with still stronger current. Thus they showed that the ocular responsive field encompassed a considerable extent of the frontal cortex and that it was not confined to any single cytoarchitectural area.

The findings of the Vogts for the frontal eye fields of Cercopithecus must not be taken to mean that this field necessarily is of the same cytoarchitectural extent in other primates. What may well prove to be major errors in our experimental evidence concerning the results of ablation or excitation of cytoarchitectural areas have come about by the general use of Brodmann's (1909) and the Vogts' (1919) maps for experiments on

other monkeys. These maps were prepared from a study of a number of brains from members of the genus Cercopithecus (in the Vogts' case, over 100 brains, species not given), and therefore it seems well to bear in mind the probability that they do not represent accurately the extent of the areas in any single individual of that genus. Any assumption that the Brodmann and Vogt maps apply equally well to the brain of members of any other genus except in a general way, seems contradicted by the findings of Richter and Hines (1938) and Walker (1940a) that area 8 in *Macaca mulatta* extends upward and onto the mesial surface of the hemisphere between areas 6 and 9. No such extension of area 8 is decided either in the cytoarchitectural maps of Brodmann and of the Vogts (figs. 95, p. 249, and 100, p. 266) or in the myeloarchitectonic map of Mauss (1908). Furthermore, cytoarchitectural areas are subject to variation in extent to such a degree that only by histological study of serial sections through the ablated area can accurate information be obtained concerning the extent of the ablation, and in many instances this procedure is necessary for the identification of the cortex beneath the stimulating electrodes. By such a study the actual extent of the lesion is recognized, and the errors caused by variation in the extent of areas, as well as the difficulties caused by differences in sulcal and gyral pattern and depth of sulci are obviated. Richter and Hines (1938) found that area 8 was subject to considerable variation from individual to individual, and therefore its extent can only be determined by careful cytoarchitectural studies. Furthermore, as these investigators remark, it seems that "the inclusion or exclusion of an apparently insignificant amount of cortical tissue at certain strategic places makes a great deal of difference in the sequelae of the operation."

No such studies as those of the Vogts on the monkey have been reported for the brain of the anthropoid apes, and one can therefore do little more than speculate regarding the cytoarchitectural fields involved. Further studies are necessary to decide whether or not the areas concerned are the same as in Cercopithecus.

In the case of man, correlation between structure and the results of stimulation or extirpation is in an unsatisfactory state, especially with regard to the frontal eye fields. C. and O. Vogt (1926), on the assumption that cortical areas in man similar in structure to those found in the monkey (Cercopithecus) were endowed with identical physiological properties, boldly transferred their cortical map for Cercopithecus to the human brain and even included the physiological characteristics of each area.

The discrepancy between the Vogts' cytoarchitectural map and that for man as given by Brodmann (1909) and von Economo and Koskinas (1925)

is striking, especially with regard to area 8 (figs. 2 and 3, pp. 11-12). For whereas the Vogts' map shows area 8 confined to a rather small strip of the cortex in the middle and inferior frontal gyri rostral to the precentral sulcus and not reaching to the medial surface of the hemisphere, both Brodmann and von Economo and Koskinas depict the cortical field possessing a cytoarchitectural structure characteristic of area 8 as continuing in the form of a broad band up to the edge of the hemisphere and extending over onto the mesial surface between areas 6 and 9 as far as the sulcus cinguli (callosomarginalis). The area named by von Economo and Koskinas in man as area frontalis intermedia, and designated as area FC, corresponds closely in position, extent, and structure to area 8 of Brodmann's map of the human cortex. On the basis of the cytoarchitectural investigations of Brodmann (1909) and von Economo and Koskinas (1925), area 8 as shown in the figures of the Vogts (1926), of Foerster (1936), and of Penfield and Boldrey (1937) is not correctly depicted (see also frontispiece). It seems probable that in man ocular movements can be elicited from all or part of Brodmann's areas 6, 8, 9, and 46, but this must be considered as tentative only and subject to revision in the light of further cytoarchitectural studies Information concerning the functional relation of these areas to each other in the production of ocular movements has been furnished by Foerster (1936). He found that ocular movements could be elicited from the foot of the middle frontal gyrus (presumably area 8) after extirpation of area 6 or after removal of the entire precentral gyrus Area 9 was found to respond with eye movements, but only when a much stronger faradic current was used, and its excitability was lost after excision of area 8.

EFFERENT PATHWAYS

The production of ocular responses by electrical stimulation of the frontal eye fields naturally raises the question as to what pathways are concerned in conveying impulses from this region of the cortex to the eye-muscle nuclei. That this region responds to electrical stimulation through the medium of its own projection fibers. which arise from cells within it and pass downward. seems proven by the fact that removal of cortex rostral and caudal to the field does not abolish its reactivity, while undercutting the area renders it unresponsive. Furthermore, degeneration studies following extirpation of a portion of area 8 with or without involvement of a portion of area 9, show that fibers from this region pass downward through the internal capsule. (See Chapter V, figs. 63 and 64, pp 137-138.)

Definite information relating to the course of the fibers conveying impulses from the frontal eye fields was reported by Brissaud (1880) From clinical and pathological investigations on hemiplegic patients, Brissaud came to the conclusion that motor impulses for voluntary contraction of all the muscles of the head and face are transmitted over nerve fibers passing through the internal capsule in the region of the genu, and that these fibers are situated in the medial part of the cerebral peduncle and end in the lower part of the brain stem.

As a result of stimulation of the internal capsule in both the monkey (*Macaca sinica*) and the orang, Beevor and Horsley (1890) found that opening of the eyes and turning of the head and eyes to the opposite side were elicitable from the posterior limb in the region of the genu at the level where the internal capsule was bounded by the caudate and thalamic nuclei medially and by the putamen laterally. The position of the nerve fibers concerned with head and eye movement was therefore shown to correspond in general to the position of the corticobulbar pathway.

Connections of the prefrontal cortex following unilateral ablation of a relatively large area in the monkey (*Macaca mulatta*), including the ocular responsive field, were described by Mettler (1935b). The Marchi method disclosed degenerated fibers passing to the caudate nucleus, the putamen, the globus pallidus, the anterior portion of the lateral group of thalamic nuclei, the substantia nigra, the corpus subthalamicus, the interstitial nucleus, the oculomotor nuclei, the rostral part of the red nucleus, the anterior tegmental nucleus, and the nucleus of the posterior commissure. The degeneration could be traced as far as the nuclei pontis where it appeared to end.

Further information concerning the course of the nerve fibers from the frontal ocular region resulted from the investigations of Hirasawa and Katô (1935) on monkeys (*Cercopithecus* from Polynesia and *Macacus cyclopis* from Formosa). Following cauterization of the cerebral cortex in the region corresponding to the Vogts' area 8αβδγ, 9e, and 9d, Marchi studies disclosed association, commissural, and projection fibers from this region. The association fibers described consisted of short fibers to the cortex of adjacent gyri and longer association fibers which passed through the external capsule to that part of the caudate nucleus forming the transition between the head and the tail. Commissural fibers were indicated by scattered degeneration in the anterior part of the corpus callosum. Corticofugal fibers were described as entering the internal capsule through the anterior limb and then occupying a position in the genu and rostral part of the posterior limb Most of the corticofugal fibers were found to end in the basal ganglia, including the head of the caudate nucleus, the putamen, the globus pal-

lidus, and the thalamus, as well as in the red nucleus, the substantia nigra, the tegmentum and the nuclei pontis. In the cerebral peduncle degenerated fibers were found in the medial part; in the pons they were present in the ventromedial longitudinal fascicuh. No degeneration was found caudal to the pons.

Degeneration of nerve fibers as revealed by the Marchi method after extirpation of a small area of cortex situated within the arc of the sulcus frontalis in the monkey (*Macaca mulatta*), and hence involving area 8, was reported by Levin (1936; see also Chapter V). He found that fibers from this region occupied the anterior extremity of the posterior limb of the internal capsule near the genu (fig. 63, p. 137) and in the cerebral peduncle were situated just lateral to the medial one-twelfth. He concluded that the fibers ended in the substantia nigra and the tegmentum. None could be traced to the superior colliculus or to the eye-muscle nuclei.

On the basis of these studies the possibility exists that in primates associated ocular movements produced by excitation of the frontal eye fields may result from impulses passing to the eye-muscle nuclei, either by way of extrapyramidal nuclei, or by a more direct pathway to the mesencephalon. Whether or not the impulses proceed thence to the eye-muscle nuclei directly or reach them through the medium of other pathways is unknown. Evidence that lateral associated movements of the eyes from excitation of the frontal cortex in the dog is produced by impulses passing over nerve fibers in the medial longitudinal fasciculus was presented by Spiegel and Tokay (1930). From further studies on the cat, Spiegel and Scala (1936) concluded that the responsible fibers in this fasciculus were ascending and arose from neurons in the vestibular nuclei. Their finding that destruction of the efferent fibers from the globus pallidus and the posterior commissure had no effect on the production of associated movements normally produced by cortical stimulation appears to refute the contention of Muskens (1934, 1937) that these structures are fundamentally concerned in the ocular responses from the frontal cortex. While severance of the medial longitudinal fasciculus or destruction of the vestibular nuclei was found to abolish horizontal conjugate movements of the eyes produced by cortical stimulation, movements of vertical conjugate deviation were still elicitable after transverse section of the brain stem just caudal to the mesencephalon. Thus they concluded that the two types of movement were mediated by separate mechanisms, the connections of the frontal cortex with the mesencephalon apparently sufficing for the production of vertical ocular movements, while connections of the frontal cortex with the vestibular nuclei were necessary for the production of horizontal ocular movements from stimulation of the frontal eye fields.

SUMMARY

In the frontal lobe of the monkey, the region from which ocular responses can be elicited by electrical stimulation is situated just rostral to the precentral gyrus. The responsive cortex extends from a short distance below the sulcus frontalis, opposite the precentral face area, upward and onto the mesial surface of the hemisphere as far as the sulcus cinguli. The response when fully developed is a complex one consisting of conjugate deviation of the eyes and turning of the head toward the opposite side, often accompanied by opening of the eyes, dilatation of the pupil, and nystagmus toward the contralateral side. The response may vary, depending on such factors as depth of anesthesia, strength of the stimulus, condition of the cortex, and general condition of the animal. A brief application of the stimulus may produce only part of the complex response. There are indications of functional subdivisions in this region, but investigators do not agree as to the way in which it should be divided. After abolition of the peripheral mechanism for horizontal conjugate movements by cutting the internal rectus of one eye and the external rectus of the other, stimulation produces vertical conjugate movements, thus demonstrating that both movements are represented in the cortex. In addition to producing activity, the frontal ocular responsive region is included in a strip of cortex which when stimulated suppresses the electrical activity of the precentral motor cortex, renders it unresponsive to electrical stimulation, and checks any after-discharge resulting from a previous stimulation (see Chapter VIII). The responsive region apparently includes cortex belonging to areas 6, 8, and 9, but the exact relation of the cytoarchitectural areas to the limits of the eye fields and the functional relation of these areas are not known.

Unilateral ablation of the frontal ocular responsive cortex in the monkey causes marked temporary disturbances characterized by deviation of the head and eyes toward the side of the lesion, circling movements toward the same side and other stereotyped activity in the somatic motor realm, an apparent contralateral homonymous hemianopsia, indifference of the animal to its environment, and an "intellectual" deficit. After bilateral ablation the animals sit motionless gazing straight ahead. The eyes follow moving objects but always return to the central position. The animals walk into the sides of the cage, and grasp any object offered them, but do not seem to know what use to make of it. After a few weeks these symptoms subside to such an extent that little remains except an expressionless face, a fixed gaze, circling movements and other restless and purposeless activity of a stereotyped character. A difference of opinion

exists as to whether or not these symptoms can be produced by extirpation of area 8 alone.

In the anthropoid apes the evidence from investigations on the chimpanzee indicates that the ocular responsive cortex occupies portions of all three frontal gyri and is situated relatively farther rostrally than in the monkey. Conjugate deviation of the eyes to the ipsilateral as well as the contralateral side accompanied by turning of the head in the same direction, pupillary dilatation, and lacrimation have been reported. As in the monkey the most rostral suppressor band includes the eye field (see Chapter VIII). Unilateral extirpation reported in one animal caused temporary conjugate deviation of the eyes towards the side of the lesion and circling movements in the same direction. No visual defect was discernible. Cytoarchitectural studies on the responsive field have not been reported.

In man ocular movements have been obtained from the frontal cortex by stimulation of the caudal part of the superior, middle and frontal gyri and the precentral gyrus. The eye movements usually consist of lateral conjugate deviation to the opposite side with or without movements of the head. Pupillary changes have not been elicited, except in one case. The cytoarchitectural areas involved probably include portions of 6, 8, 9, and possibly 46, but accurate information regarding this is not available at present. Irritative lesions involving the frontal eye fields on one side may cause either constant lateral deviation to the opposite side or epileptic attacks characterized by clonic movements of the eyes toward the opposite side, followed by motor phenomena elsewhere in the body. Unilateral acute destructive lesions involving the frontal ocular cortex or its efferent fibers as they pass through the internal capsule, produce temporary conjugate lateral deviation to the same side and inability of the patient to move the eyes toward the opposite side on command. The head may be turned in the same direction. Reflex movements of the eyes depending on visual impulses encompass the normal range through the mechanism of the visual fixation reflex. Movements of the eyes away from an object that has been fixed upon may not be possible until the foveal impulses have been extinguished. Bilateral lesions of the efferent fibers ocurring in pseudobulbar palsy result in a fixed central gaze and inability to move the eyes voluntarily, but reflex movements may be well performed.

The evidence available indicates that efferent fibers from the frontal ocular cortex pass through the region of the genu of the internal capsule to a number of extrapyramidal nuclei. In addition, some fibers have been traced into the mesencephalon, but none have been followed into the eye-muscle nuclei, and none appear to pass beyond the pons. From experi-

ments on animals below primates, evidence has been obtained to show that impulses from the frontal cortex causing conjugate lateral movements of the eyes pass to the vestibular nuclei and then to the eye-muscle nuclei over ascending fibers in the medial longitudinal fasciculus. On the other hand, the pathways for the production of vertical conjugate movements from cortical stimulation were found not to extend lower than the mesencephalon.

The frontal ocular field seems not only to provide for voluntary movements of the eyes, but it appears to be concerned with influencing the visual fixation reflex, chiefly in the form of releasing the motor apparatus of the eyes from its control, thus permitting the eyes to become fixed on other objects.

Chapter XIII

ELECTRICAL EXCITABILITY IN MAN

Theodore C. Erickson, A.M., M.D., M.Sc., Ph.D.

Associate Professor of Surgery
University of Wisconsin
Madison, Wisconsin

ELECTRICAL EXCITABILITY IN MAN

ITZIG (1870) PRECEDED his animal experiments by galvanic stimulation applied through electrodes on the mastoid processes or ear lobes of man, thus producing eye movements and dizziness, which he concluded were central in origin. Direct stimulation of the cerebral cortex of man was first carried out by Robert Bartholow (1874), a surgeon of Cincinnati. His patient presented an ulcer of the scalp which had eroded the skull. By faradization of the exposed dura mater "with the least possible current," Bartholow induced muscular contractions of the opposite arm and leg with head turning. Passing the electrode into the brain substance and using a stronger current, he produced a convulsion on the contralateral side and the patient became unconscious. Three days after this procedure and following a series of right sided convulsions the patient died. Fortunately subsequent studies of cortical excitability have been less hazardous.

Observations on the electrical excitability of the human cortex have always been limited by the clinical opportunities presented to the physiologically minded surgeon. Investigation of the motor cortex in man has tended to follow the leads furnished by animal experimentation. With the development of modern neurosurgery, however, the number of observations multiplied rapidly. In the period between Bartholow's report of 1874 and the year 1914 seventy-four cases were recorded in which the brain was electrically stimulated at the operating table. An excellent bibliography on the subject is to be found in a recent paper by Scarff (1940). There is no reason here to review this literature in detail, for most of these observations in the human corroborated the work previously reported in animals. Where their data were insufficient for the preparation of cortical maps, many earlier surgeons made liberal use of the observations on anthropoid apes and lower animals. On the other hand, the Vogts (1919, 1926) prepared a map of the human cerebral cortex on the basis of their comparative cytoarchitectonic studies and electrical stimulation of the monkey's cortex. This map corresponded to a surprising extent with that prepared by Foerster (1926b, 1936b) as the result of stimulating the cortex of almost three hundred patients under local anesthesia. The chief remaining contributor to this field of knowledge is Penfield, who with Boldrey (1937) reviewed the results of cortical stimulation carried out under local anesthesia in 163 craniotomies. Scarff (1940) has recently reported fourteen cases studied with special reference to the location of the centers for the lower extremity.

It may not be amiss to refer to the practical value of electrical stimulation to the neurosurgeon. Grossly it is difficult to identify the central sulcus, even in the anatomical laboratory with the pia arachnoid removed so as to render the sulci prominent. During operation, with the arachnoid intact and only a limited portion of the hemisphere surface exposed, it is virtually impossible to identify the central sulcus with certainty The great anastomotic vein of Trolard, often considered as a guide, ascends sometimes in the central sulcus and sometimes in the postcentral sulcus; but again its size as well as position is variable Electrical stimulation is the only certain method of achieving exact localization during operation, and as such is of great practical value when removal of lesions in the vicinity of the motor area is contemplated In the epileptic patient such stimulation also helps to confirm the location of an epileptogenic focus by reproducing the patient's habitual seizure. These must be carefully distinguished from so-called "physiological seizures" or "after-discharges" produced by stimuli of excessive duration or intensity (Penfield and Erickson, 1941).

Since electrical stimulation is not usually performed on normal individuals, the question arises as to how the patient's disease may influence the results. Most of the studies have been carried out in epileptics and, barring any distorting lesion, the responses to stimulation within the precentral motor area with certain exceptions are the same as in normal individuals Before or after seizures these patients may exhibit marked facilitation of response, or on the other hand complete inhibition. Another effect presumably characteristic of the epileptic is the activation of remote areas of the cortex not ordinarily responsive to stimulation (Penfield and Boldrey, 1937).

The choice of the proper anesthetic agent is of the greatest importance when study of the cortex by means of electrical stimulation is contemplated Deep general anesthesia with almost any agent will render the cortex relatively inexcitable and for this reason local anesthesia is to be preferred whenever possible. Nupercaine (1/1500 and 1/4000) solution is especially suitable (see Penfield and Erickson, 1941). When the patient is a child or is especially uncooperative, however, general anesthesia is necessary. Cortical excitability is sometimes well preserved with avertin. From my recent experience it appears that intravenous sodium pentothal may be used during the initial stages of the operation while the scalp, bone flap, and dura mater are being reflected If a local anesthetic has been injected, the patient may then be allowed to regain consciousness; the cortical excitability returns rapidly, so as to permit satisfactory results from stimulation.

No histological changes in the nerve cells or neuroglia have been demonstrated following careful electrical stimulation within the usual effec-

tive ranges. Stronger stimulation of the exposed cortex of the cat or the dog may, however, cause a focal cerebral ischemia through spasm of the pial vessels (Echlin, 1942). The pial vessels of man are apparently less susceptible to the induction of such spasm.

Various types of electrical current have been used for cortical stimulation. Although galvanic stimuli were first employed by Fritsch and Hitzig, faradic current used by Ferrier has been commonly employed since then. In the past decade thyratron stimulators have been popular because of their stability and reliability, while others have employed a sinusoidal wave stimulator. The relative merits of these and other forms of stimulators have been recently discussed by Erickson and Gilson (1943)

A duration of one second or less is usually sufficient to produce discrete and unsustained responses from the sensorimotor cortex. If the duration is prolonged to 5 or 10 seconds, the tendency to produce an after-discharge is increased; that is, the response outlasts the stimulus by an appreciable length of time and constitutes an epileptiform seizure which spreads along definite neural pathways (Erickson 1940). It must be kept in mind that with increased duration of stimuli there is an increasing possibility of cortical damage which is not present with stimulation of shorter duration.

The optimum frequency for stimulation of the cerebral cortex has been variously stated to lie between 25 and 90 stimuli per second. Possible regional differences between the various cortical areas in this respect have not been investigated Hines (1940) found that 90 cycles per second were optimum for the chimpanzee, while 60 per second have been extensively used and are quite satisfactory for obtaining responses from the human cortex. Few studies have been made of the optimal wave shape for cortical stimulation. For single stimuli, Wyss and Obrador (1937) found that optimum current duration was obtained with a rising phase between 7 and 20 milliseconds; whence they concluded that ordinary induction shocks are much too short to be considered as adequate stimuli for cortical motor elements.

The detailed technique of using electrical stimulation in the operating room has been described elsewhere (Penfield and Erickson, 1941). It is important to begin with a subliminal stimulus and gradually increase the intensity until a response is obtained, using a duration of one second or less so as to avoid after-discharge.

Penfield and Boldrey (1937) analyzed the results obtained in 163 craniotomies. and the following discussion is largely based upon their results except where otherwise stated. Motor responses (fig 113) occurred almost exclusively from the pre- and postcentral gyri, and by far the greatest number were situated on the anterior brim of the central sulcus. No increase of current strength was required to evoke the responses from

the postcentral gyrus, so they cannot be attributed to spread of the stimulating current. Numbness, tingling, or a sense of movement, while usually obtained from the postcentral gyrus, not infrequently resulted from stimulation of the precentral gyrus, thus emphasizing the close functional relationship of corresponding parts of these gyri. All responses were eliminated in which there was a so-called "physiological seizure," that is, an "after-discharge" or continuance of the response after cessation of the stimulus. No evidence of the tertiary motor area described by the Vogts as 6aα or of the various extrapyramidal motor areas proposed by Foerster was obtained. Rather, the results resembled those obtained by Grünbaum and Sherrington (1903) in the chimpanzee.

The contralateral nature of most movements resulting from electrical stimulation has been universally recognized. The occurrence of ipsilateral movements in man is, on the other hand, rare. Bucy and Fulton (1933) in their study of the ipsilateral responses obtained from the monkey's cortex refer to a few such instances. Other neurosurgeons with a large experience have not observed ipsilateral movements. It is possible that being unusual they may have been mistaken for voluntary movements of a restless pa-
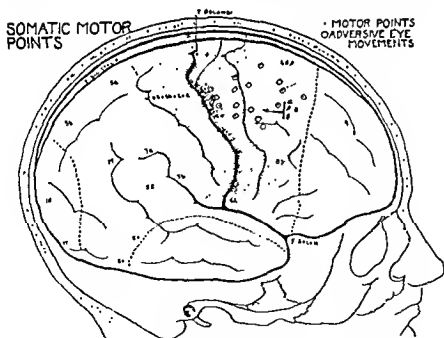
Fig 113—Somatic motor points obtained on stimulation of human cerebral cortex (from Penfield and Boldrev, 1937) Each dot represents a motor response obtained from patients under local anesthesia

tient. Specific observation has apparently not been directed to the ipsilateral extremities and, since they are not of such a dramatic nature as are the contralateral movements, they may be overlooked.

Although there is a bilateral cortical representation of certain midline structures such as the tongue, the movements produced by electrical stimulation are almost always contralateral. While the trunk and neck evidence no detectable paralysis after a unilateral cortical lesion, stimulation often produces movement on the contralateral half. Other foci, for example those of the larynx and palate, respond to stimuli of lowest intensity only with bilateral movement.

Sequence of Motor Representation on Precentral Cortex
(Modified from Penfield and Boldrey, 1937)

Toes	
Ankle	} *Medial Surface of Hemisphere*
Knee	
Dorsomedial Margin of Hemisphere	
Hip	
Back	
Shoulder	
Elbow	
Wrist	
Hand	
Little Finger	
Ring Finger	
Middle Finger	} *Lateral Surface of Hemisphere*
Thumb	
Brow Eye	
Eyelid Movements	
Vocalization	
Lips	
Jaw	
Tongue	
Swallow	
Fissure of Sylvius	

Right Central Sulcus
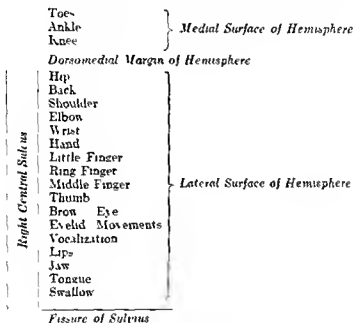
The sequence of motor representation on the precentral gyrus is constant from patient to patient as shown on the accompanying diagram; that is, if movement of the thumb is obtained, it is from a point closer to the fissure of Sylvius than a point giving rise to movement of the index or the little finger, and so on. On the other hand, the point giving rise to thumb movements may be situated much further from the fissure of Sylvius in one individual than in another; so that if the responses from a large group of patients are plotted on one cortical map, there is spread of the responses over a wide area as shown in fig. 114. The variable location in different patients of this motor sequence keyboard in respect to the fissure of Sylvius and the interhemispheral fissure is nowhere so striking as in the leg and foot areas. Arm responses may be obtained up to the longitudinal

fissure, but stimulation of the upper portion of the precentral gyrus resulted in leg movements in twenty-three instances (Penfield and Boldrey, 1937). Two leg responses were obtained from the medial surface of the hemisphere. Due to the inherent surgical difficulties of approaching this latter region, the number of observations has been small. Scarff (1940) obtained no responses in the lower extremities on stimulation of the lateral surface of the hemisphere in fourteen patients. In one patient he did produce leg movements from stimulation of the medial surface of the hemisphere. On the basis of these cases and the negative evidence of his excellent review of the literature, he contends that leg centers are represented only on the mesial surface of the hemisphere and arm representation extends to the superior mesial border of the hemisphere.

There can be little doubt that the paracentral lobule "contains the foci of the foot, of the toes, of the bladder, and of the rectum" (Foerster, 1936a, p 137); but, as amply demonstrated in Penfield's results, there is also representation of leg areas on the upper part of the precentral and postcentral gyri. This is but an illustration of the overlapping of foci. No focus is exclusive for any one part of the body but rather represents, to a lesser extent it is true, many adjacent portions. According to Hughlings Jackson's
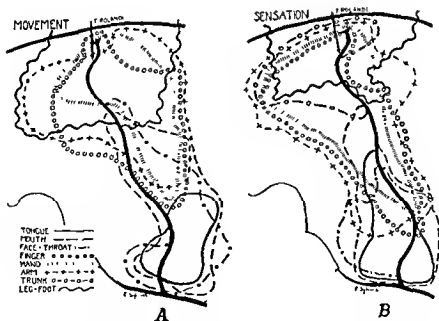
Fig 114—Outline of areas giving motor and sensory responses (from Penfield and Boldrey, 1937). The area from which responses of the leg and foot were obtained extends over into the longitudinal fissure upon the medial surface of the hemisphere.

doctrine a single part of the body, say the big toe, is represented preponderantly in one part of the cortex; but it is represented on other parts of the pre- and postcentral gyri as well Maps of the human cortex have some of the failings of maps of the world, resulting from the inherent difficulty of projecting curved planes onto flat surfaces. Even more formidable is the task of representing the overlapping and interrelated functions of the motor cortex on a single conventional motor map. The extent of overlap is no doubt reflected to a certain extent in the wide areas from which the same part gives responses as shown in fig 114.

The relatively large extent of the finger areas on the precentral gyrus is striking. In contrast to the toes which rarely if ever move singly, each finger has its special localization Penfield and Boldrey (1937) found that finger movements were among the best localized responses The responsive points extended $3\frac{1}{2}$ cm. along the length of the central sulcus, while very few were found more than 1 cm distant from it We have here an illustration of the fact, pointed out very long ago by Hughlings Jackson, that representation in the motor cortex depends not upon the size of the muscles of a part of the body but rather on the number and intricacy of their movements

Vocalization as a response to stimulation of the precentral gyrus was first obtained by Penfield, and in 1938 he reported six cases in which this had been produced. It was observed equally frequently in the dominant and in the nondominant hemisphere and was localized in a restricted portion of the precentral gyrus between the areas for eyelid movements above and for mouth movements below. This vocalization did not resemble the grunts previously reported by Foerster and others. Rather, there was a loud, continuing cry with nothing to suggest the formation of words. It has been pointed out that this vocalization bears no more resemblance to speech than a twitching of the finger, induced by stimulation or a seizure, does to skilled purposeful movements of the hand.

Conjugate deviation of the eyes to the contralateral side occurs following stimulation of an area roughly corresponding to area 8. Upward deviation of the eyes has also been frequently seen in contrast to the rarity or absence of downward deviation Adversive movements of the head and eyes together were found by Penfield in the general area of face representation on the precentral gyrus. Using minimal intensity of stimulation, he obtained no such movements from area $6a\beta$ (of the Vogts) as were described by Foerster. It seems probable that such mass movements are brought into play only by an epileptiform discharge induced by a greater intensity of stimulating current.

No reference is made here to autonomic responses, which are reviewed in Chapter XI.

Secondary facilitation has been demonstrated in the human motor cortex similar to that which has long been known in animals.

The type of movement resulting from stimulation of the human cortex has perhaps not received as much attention or careful analysis as it deserves. The primary interest has been in localization of the various parts of the body in the cortex. Simple twitches of an isolated muscle are observed, but the response may be the fragment of a complex movement involving several groups. It has been said that movements rather than muscular units are represented in the precentral cortex. However, the responses elicited by our electrodes are only fragments of movements which have not been organized into functional units. They are more closely related to the uncontrolled useless contractions of the epileptiform seizure than they are to the normal purposeful voluntary movements.

In conclusion we can only admit that there remain many problems concerning electrical stimulation of the cortex yet to be solved. Pure localization studies of somatic motor movements have no doubt been carried to their greatest limits of accuracy with the methods of stimulation at present available. Study of other types of response with new and better tools may reveal the organization of this area in man with greater clarity. Since the opportunities for pursuing these investigations are limited by clinical conditions, it is especially important that the neurosurgeon be thoroughly cognizant of the results of animal experimentation which light the way for those problems which can be solved only in man.

Chapter XIV

EFFECTS OF EXTIRPATION
IN MAN

Paul C. Bucy, M.S., M.D.

Professor of Neurology and Neurological Surgery
University of Illinois College of Medicine
and
Attending Neurologist and Neurological Surgeon
Illinois Research and Educational Hospitals
and The Chicago Memorial Hospital
Chicago

OUTLINE OF CHAPTER XIV

Extirpation in Man

I. Review of Previous Reports

II. Clinical Observations

III. Conclusions

M UCH OF OUR KNOWLEDGE of the functional activity of the human precentral motor cortex has been accumulated by inference from animal experimentation and from human cases in which the projection fibers from this region have been destroyed in the internal capsule or elsewhere. Although much has been learned by means of electrical stimulation, as in the excellent observations made by Foerster (1936), Penfield and Boldrey (1937), and others, this method has serious limitations, and the results obtained from apes and other animals can not be applied in their entirety to man. Subcortical lesions though they may destroy the projection fibers from the precentral motor area also destroy other fibers and often other cellular areas, thus making them unacceptable as conclusive evidence regarding the activities of this region. Electrical stimulation can be regarded only as a very poor substitute for normal physiological activity. For instance as Penfield and Erickson (1941) have noted, "The type of movement that suffers most as the result of a [precentral] convolutional injury [i.e., delicate or skilled movements] is never reproduced by artificial stimulation."

REVIEW OF PREVIOUS REPORTS

Obviously a study of the effects of extirpation of the precentral motor cortex from individuals with no pre-existing disease would greatly enhance our knowledge, as it has in animals. But, naturally, no such studies have been or are likely to be made. Observations of the effects of such extirpations upon human beings with disease but with little or no paralysis, spasticity, or reflex changes of the contralateral extremities would supplement our knowledge considerably, but even these are almost non-existent. Penfield (1940) writes that except for the right "face" area—and, I gather from his book with Erickson (1941), small parts of the leg area—he has never removed any part of the precentral gyrus under such circumstances. The only detailed report of this type which I have been able to find is that of Horsley (1909). This valuable observation has been too long ignored, and I shall present it here in some detail.

Horsley (1909)

He was a well-developed boy 14 years of age, who had suffered from athetoid movements of the left upper extremity for seven years. When the limb was quiet, his purposive or voluntary movements were normal and powerful. The reflexes, superficial and deep, were everywhere normal and all forms of sensation were intact.

On March 20, 1908, the right central region was exposed. The cortex was stimulated

electrically and motor responses in the left upper extremity were elicited only by stimulation of the precentral gyrus. These movements were of the face, thumb, fingers, wrist, elbow, and shoulder. The precentral gyrus was then removed by subpial dissection.

The involuntary movements were abolished by this operation and were still absent one year later.

Sense of position in the left upper extremity was completely lost for two weeks after the operation and then began to return but never was recovered completely. The perception of light touch and pin-prick were at first impaired but later recovered almost completely. The appreciation of differences in temperature was diminished peripherally at first but later recovered and was replaced by a slight hyperesthesia. The recognition of the form of objects was markedly impaired and continued so for over a year.

The left upper extremity was flaccid and

perfectly motionless for 14 days after the operation. On the 14th day slow involuntary movement of the left forearm, wrist, and fingers was observed in association with forceful voluntary grasping movements of the right hand. At the end of the third week after the operation, voluntary movement returned to the shoulder; later, flexion and extension of the elbow and flexion of the wrist returned. Even later movement returned to the thumb and fingers and about 13 months after the operation he could slowly flex and extend the thumb. Ability to extend the fingers was present in rapidly diminishing degree from the index to the ring finger and the little finger could not be extended at all. The fingers could be flexed, but evaluation of the amount of voluntary flexion was complicated by the flexor hypertonia. He was able to use the extremity as a help in dressing but found that it was not useful in the performance of "two-handed work."

From his observations Horsley concluded that the precentral gyrus performed both sensory and motor functions, that the giant pyramidal or Betz cells are not essential for the performance of purposive or voluntary movements and that such movements can be performed after complete removal of the corresponding part of the precentral gyrus.

Sachs (1935)

A series of similar operations, in which segments of the precentral gyrus were removed, was reported in considerable detail by Sachs (1935):

In Case 1 the arm was flaccid and areflexive immediately after extirpation of the "arm centre." In Case 2 removal of the "arm" area resulted in only temporary moderate weakness of the hand. In Case 7 removal of the "arm centre" resulted in a complete spastic paralysis of the arm, forearm, and hand. In Case 8 the extent of the extirpation is not stated. Immediately following the operation the arm and leg were

completely paralyzed. One year later he used his hand perfectly but it was "dumb." Case 10—no statement as to area removed—presumably "arm centre." Complete loss of movement of arm; reflexes normal; no flaccidity. Recovery began after 24 days but never became complete. For various reasons cases 3, 4, 5, 6, 9, and 11 are not suitable for elucidation of this matter

Walshe (1935)

Walshe reported a case in which removal of the "leg" area of the right precentral gyrus was followed by a spastic paralysis of the left lower extremity. He interpreted this as proving that destruction of the precentral gyrus or the area gigantopyramidalis alone results in a spastic paralysis. Without denying the possibility that this may be true, it should be pointed out that neither this nor any other case yet available clearly establishes

the nature of the paralysis which follows the isolated destruction of area 4 in man. In this case cited by Walshe, Mr. Taylor made his extirpation with a "diathermic knife." It is well known that the high frequency electrical surgical instruments damage tissue for some distance on both sides of the incision. With such an instrument the damage can not be confined to the block of cortex which was extirpated. That this is true in this case is clearly shown by the fact that although the extirpation was presumably limited to part of the representation of the lower extremity in the precentral gyrus, there was a definite paresis of both the upper extremity and the face following the operation.

Foerster (1936)

Foerster (1936b, pp. 144-199) discusses in great detail the results of excision of the various parts of the precentral gyrus. Unfortunately details of individual cases are completely lacking and we are not informed about the condition of the patients prior to operation, the condition of their brains, nor the extent of the operations. The results are presented as a summary of his entire experience. He states that the immediate result of such an extirpation is a complete flaccid paralysis and areflexia. The Babinski response appears within 5 to 10 hours and the knee and ankle jerks in 2 or 3 days. The tendon reflexes in the arms remain absent longer, at times for 14 days. After about 15 days, the flaccidity gradually gives way to spasticity. The complete paralysis lasts for 10 to 14 days in the leg and somewhat longer for the upper extremity. Functioning ability then returns though with impaired voluntary power. The isolated movements to a large extent remain abolished, and the movements consist primarily of "synergies." In the "flexor synergy" simultaneous flexion and abduction of the thigh, flexion of the knee, dorsi-flexion and supination of the foot, and dorsi-flexion of the toes occur. Thus, if the patient attempts dorsi-flexion of the foot, flexion of the knee and hip also occur, or if he flexes the knee, the related movements occur at the hip, ankle, and toes. "The components of each synergy are inseparable," and individual components of a synergy can not be produced alone. A component of one synergy is never combined with that of another. Fine movements of the fingers are lost as well as isolated movement of individual fingers.

The muscles of the lower extremity are more extensively represented in the ipsilateral cortex than are those of the upper extremity. Foerster is unable to agree with Kleist (1934) and with Penfield and Boldrey (1937) that the only muscles which are represented in both cerebral hemispheres are those in which voluntary bilateral symmetrical activity occurs, such as those of the trunk, neck, eyes, upper face, throat, larynx, diaphragm, bladder, and rectum (Foerster, 1936b, p. 242). After removal of the trunk

area the abdominal and cremasteric reflexes are initially abolished but return after 7 to 10 days though they remain weaker than on the healthy side. In two cases of bilateral cortical paralysis of the lower extremities the abdominal reflexes disappeared and remained absent.

Foerster observed that after excision of the precentral gyrus there was a considerable sensory loss but this soon disappeared and was not persistent in any case.

Putnam (1940)

Putnam (1940) reported two cases. In Case 1 there was an alternating tremor at rest but no weakness, rigidity, or abnormality of reflexes. The "arm" area of the precentral gyrus was removed There was a flaccid paralysis of the arm, without sensory changes, which gradually improved. Four months after the operation there was little weakness but marked awkwardness. In Case 2 there was marked tremor. The grasp was powerful and there seems to have been little weakness or abnormality of reflexes. A narrow strip of cortex, 2 cm. long, 0.4 cm. wide and 0 6 cm deep, was removed from the posterior part of the precentral gyrus in the arm area. Voluntary movements began to return to the arm after four days, and at the end of three weeks she could feebly make a fist. Six weeks after the operation she could raise her hand above her head and "use it for many purposes." There was a definite "lead pipe" rigidity in the fingers, wrist, and elbow.

CLINICAL OBSERVATIONS

Portions of the precentral motor cortex have been removed from a number of individuals (Bucy, 1940). In the majority of instances, however, the contralateral extremities were already involved by a considerable spastic paresis. In only four cases were voluntary control, strength, reflexes, and sensation nearly normal, thus making them suitable for analysis of the effect of extirpation of part of the precentral motor cortex. Even in these cases the extremities concerned were not normal, as in every instance they were so involved by involuntary movements as to render them almost useless and to cause the patients to seek relief by surgical means.

In no instance was the entire precentral motor cortex removed from one hemisphere. In one case a large part of the "leg" area was removed, in two the "arm" area was extirpated, and in one the "arm and leg" areas were removed.

CASE 1

M P P (223601), a female, twenty-three years of age was referred to me by Dr Hans H Reese of Madison Wisconsin She was admitted to the University of Chicago Clinics on July 10, 1939 suffering from convulsive seizures

She was born on September 17, 1915, following a long and difficult labor However she appeared well until the age of eighteen months when she had six generalized convulsions When ten years old she began to suffer from convulsions which involved only the right leg and occurred at night while she was asleep Io 1934, at the age of nineteen years, the attacks involved the entire right side and in 1939 the attacks, which always began with flexion of the right knee occurred in the daytime as well as at night All of the usual anticonvulsant remedies tried over many years brought no improvement.

She was well-developed, alert intelligent, and cooperative The general physical examination was negative Neurological examination was negative except that rapidly alternating movements were less well performed with the right hand and she was unable to hop on the right foot alone

Roentgenograms of the skull revealed no abnormality and pneumoencephalograms demonstrated a normal ventricular system, but there was somewhat more than the usual amount of gas in the subarachnoid

spaces over *both* parietal lobes Urinalysis, blood counts, Wassermann and Kahn tests on the blood, and examination of the spinal fluid all gave normal findings

Electroencephalograms were made on two occasions by Dr T J Case They appeared normal except for the occurrence of small spike-like waves obtained from leads placed in the superior part of the left posterior frontal region None of the wave patterns common to victims of idiopathic epilepsy was seen

Operation

On July 13, 1939, under tribromethanol in amylene hydrate (90 mgm per kg of body weight) later supplemented by additional avertin (20 mgm per kg) and a small quantity of ether, the central region of the left cerebral hemisphere up to the interhemispheric fissure was exposed The cortex appeared normal except that the sulci in the anterior part of the precentral region were wider than normal and filled with fluid which communicated freely with the remainder of the subarachnoid space There
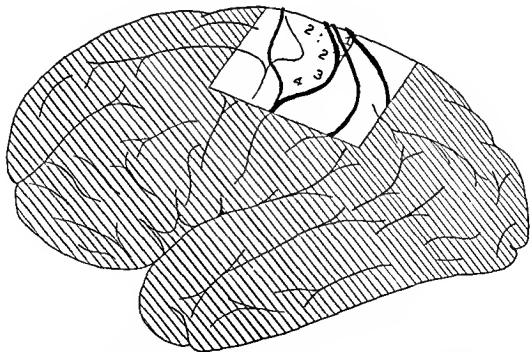
Fig 115 (Case 1).—Clear area indicates the field exposed at operation The veins are shown by heavy black lines Electrical stimulation resulted in flexion of the right thigh at the hip from the region marked *1*, no response from *2*, and movement of the right upper extremity from *3* and *4* The square area enclosed by dotted lines and including area 1 was extirpated

were numerous large veins passing to the superior longitudinal sinus which crossed the uppermost part of the precentral gyrus, completely covering this region except for a small area about 4 mm square (fig 115)

With a sixty-cycle sinusoidal current of an intensity of seven volts, the exposed cortex was stimulated, only the precentral gyrus was excitable, and all movements which were produced were in the (contralateral) right extremities Movements of the fingers, forearm, and upper arm were elicited Medial to the area from which these were produced was an inexcitable area It is noteworthy that though movements of the abdominal wall were looked for none were observed. Above this inexcitable area, the veins noted above interfered with adequate electrical exploration of the most medial part of the precentral gyrus Stimulation of the small area of cortex on the lateral surface of the hemisphere in this region, which was visible between the veins, evoked flexion of the thigh at the hip but no other movement in the lower extremity could be produced

The uppermost part of the precentral gyrus, including part of the paracentral lobule was removed piecemeal from beneath the cortical veins, leaving them intact

Post-Operative Course

She made a rapid and uneventful recovery from the operation and was discharged to her home on the eighth post-operative day, July 22, 1939 To date, approximately four years later, she has continued with her anticonvulsant medication and has had no convulsive seizures of any kind She has recently been married

On the day of operation, a slight right facial weakness was noted, but it practically disappeared later that day and was barely perceptible when she was discharged eight days later There was never any other abnormality in the domain of the cranial nerves

At no time was there any more than the slightest weakness in the right upper extremity On August 15, 1939, thirty-three days after the operation, she wrote that her writing, with the right hand, was not as good as before the operation, and on comparing samples of her writing, it was obvious that it was slightly coarser than before but not otherwise different On August 30 the forty-eighth post-operative day, her family physician, Dr V E Eastman of Wausau Wisconsin, wrote that the strength

in her right arm was 85 percent of normal Since then the arm has seemed entirely normal to her Throughout her eight-day stay in the hospital after the operation, the tendon reflexes were more active in the right arm than in the left On the second post-operative day, there was a definite increase in resistance to passive movements of the right upper extremity, but this was not again observed

On the first post-operative day, voluntary movements at the right hip and knee were relatively strong, but she was unable to move the foot or toes This was still the case on the fourth post-operative day On the fifth she walked, limping on the right foot On the eighth post-operative day, there was moderate weakness of movements of the right hip and knee, as compared to the left. She was able to make all movements of the foot at the ankle, though they were moderately weak, dorsiflexion and eversion being weaker than plantar extension and inversion The toes could be flexed and extended and their strength was estimated at 60 to 70 percent of that of the left. On the thirty-third post-operative day, she wrote stating that the right foot did not always do what she wanted it to but that no one could detect any lameness when she walked On the forty-eighth day, Dr Eastman estimated the strength in the right leg at 85 percent of normal She was able to walk eight or ten blocks with only moderate fatigue On the sixty-first post-operative day, she returned to her clerical work On August 20, 1940, thirteen months post-operative, she wrote, "There is a slight weakness of the right leg only but so slight that it is not at all noticeable and causes me no trouble I skated last winter (1939-1940), biked, and danced this summer—in fact everything I had been used to doing" On May 20, 1941, about twenty-two months after the operation, she wrote, "I have complete control of my right foot and leg at all times When I tire they seem to be the most tired, but I do everything that any other person does I walk without a suspicion of a limp and I walk a good deal We skated quite a bit last winter, and we dance quite a bit I do all these things with perfect freedom"

On the first post-operative day, the tendon reflexes were more active in the right lower extremity than in the left and remained so throughout the remaining days in the hospital Plantar stimulation evoked fanning of the little toe on the right foot and dorsiflexion ("extension") of the leg

toe Babinski's sign was still present when she was discharged

The abdominal reflexes were apparently not examined until the eighth post-operative day, when they were all present, active and equal Sensation, light touch, pin-

prick, vibration, and position sense were all intact on the eighth day but were apparently not examined earlier

At no time were any alterations in cutaneous temperature or in the cutaneous vascular bed noted

Comment on Case 1

In this case, as in almost all others in my experience, stimulation of the most superior part of the precentral gyrus on the lateral surface of the hemisphere elicited movement in the lower extremity only at the most proximal joint, the hip Thus, my observations would in the main support Scarff's (1940) contention that the greater part of the lower extremity is represented elsewhere, presumably in the paracentral lobule on the medial surface of the hemisphere However, such a contention can not be too readily accepted. First, there is little positive evidence in its support; movements of the knee, ankle, and toes have rarely been produced by stimulation of the medial surface In my cases at least, stimulation has been carried out under ether anaesthesia, not the ideal circumstances for examining the electrical excitability of the cortex. Most important of all, the upper part of the precentral gyrus is covered by a tangle of veins making complete exploration of this region impossible. If the veins are destroyed, removed, or displaced, so as to expose this area adequately the excitability of the cortex is so distributed as to render negative observations of even less value than usual.

In Case 1 it can not be supposed that the entire "leg" area of the precentral motor cortex (areas 4 and 6) was removed As it was removed piecemeal, an accurate delimitation by microscopical examination, of the area destroyed was impossible It appears that the extirpation included most of area 4γ of the "leg" area on both the lateral and medial surfaces It is unlikely that much, if any, of area 6 was destroyed. Nevertheless, the partial and very temporary nature of the paralysis which developed in the contralateral lower extremity is in striking contrast to the paralysis that develops in the upper extremity following removal of the "arm" area. Although what the nature of the paralysis in the upper extremity would be after removal of only area 4γ from the "arm" area has never been tested except in Putnam's (1940) Case 2 (p 358).

CASE 2

E S (226850), a young man, twenty-one years of age, was referred to me by Dr P H Harmon of Springfield, Illinois He was admitted to the University of Chicago Clinics on two occasions, from August 27th

to August 30th, 1939, and from December 4 1939, to January 19, 1940

He was severely injured in an automobile accident on October 18, 1935, and shortly thereafter developed severe jerking

involuntary movements in the left arm
He was unable to perform fine movements
with the left hand but could pick up
objects and do heavy work

Physical Examination

The general physical examination was
negative He was a well-developed mus-
cular man The left palpebral fissure was
slightly wider than the right, but this was
the only evidence of any facial weakness
He was unable to shrug the left shoulder
as well as the right There was a mild
weakness of all movement in the left upper
extremity and an even slighter weakness of
the left lower extremity. Tendon reflexes
could not be accurately examined in the
left upper extremity because of the invol-
untary movements but they were not
grossly exaggerated Hoffmann's sign could
not be elicited The abdominal reflexes
could all be obtained, but they were slightly
less active on the left side The knee and
ankle jerks were present and equal bilater-
ally Babinski's sign was not present.

Sensation was everywhere intact but over
the entire left half of the body pin-prick
and cotton produced an unpleasant tingling
sensation

Except for a very rare involuntary move-
ment in the left leg all abnormal move-

ments were confined to the left upper
extremity. The entire extremity was in-
volved and no part more severely than
another The movements were variable.
They did not follow any constant sequence
and involved various parts of the ex-
tremity at random Each individual move-
ment was quick and jerky, sudden in onset
and short in duration However, they fol-
lowed each other in such rapid succession
that the extremity was constantly in a state
of violent activity The condition was
classified as hemiballismus or choreo-
athetosis

The usual laboratory examinations on
urine, blood, and spinal fluid were all
negative A pneumoencephalogram was
made The right lateral ventricle was a
little larger than the left and its floor was
depressed indicating an atrophy of the
ganglionic structures in that region

Operation

On December 9, 1939, under light ether
anæsthesia an osteoplastic flap was re-
flected, exposing the central area of the
right cerebral hemisphere up to the inter-
hemisphere fissure The meninges and
cerebral cortex appeared to be normal The
entire exposed cortex was stimulated with
an alternating 60 cycle sinusoidal current of
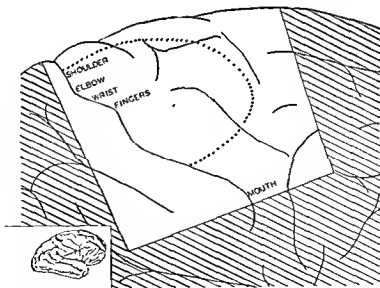
Fig 116 (Case 2)—Diagrammatic sketch of the field exposed at operation, summarizing
the results of electrical stimulation and indicating, within the dotted line, the area extirpated

five or six volts A bipolar electrode was used. Responses were elicited only in the left upper extremity and left side of the face They were obtained only from the posterior part of one gyrus which was accordingly judged to be the precentral There were two separate excitable areas separated by an inexcitable area From the lower and smaller area movements could be produced in the left side of the face, particularly about the mouth From the more superiorly placed field we obtained movements of the left upper extremity in the shoulder, elbow wrist and fingers The uppermost part of this gyrus was inexcitable However, as a small area of cortical schema had been produced in this area when coagulating a vessel in the overlying dura mater, this inexcitability is not necessarily significant

That portion of the precentral gyrus from which movements in the left upper extremity were elicited the upper half of the inexcitable field lying between the 'finger' area and the 'face' area and the posterior parts of the neighboring frontal gyri were excised (fig 116) Posteriorly the excision included all of the anterior wall of the rolandic fissure The extirpation was only sufficiently deep to insure the removal of all cortex and included the immediately subjacent white matter Small amounts of cortex lying at the bottoms of sulci were removed by suction The cavity left by this extirpation was deepest posteriorly where it measured 2 cm On the surface of the brain it measured 4 cm along the rolandic fissure, 3 cm antero-posteriorly parallel to the interhemispheric fissure. 2 cm along the inferior margin and 2 7 cm along the anterior margin

Microscopic Examination

Simple sections oriented antero-posteriorly were cut from the block at about every 6 to 7 mm The posterior part of the block had been removed by subpial dissection and therefore severely traumatized, much of it being lost It is, therefore not surprising that no Betz cells are seen in any of these sections The cortical tissue contained in these sections is typical of the precentral agranular cortex without Betz cells, i.e., areas 4s, 4s, and 6 It is essentially normal in appearance except that in some areas the number of pyramidal cells in layer III appears to be reduced There is no evidence of inflammation The leptomeninx is normal

Post-Operative Course

The involuntary movements were completely abolished immediately after the operation They were still absent when he was discharged from the hospital on January 19, 1940 forty-one days after the operation Shortly thereafter some slight involuntary movements returned to the left fingers When seen on October 12 and 14, 1940, ten months after the operation the involuntary movements were absent 95 percent of the time They were practically limited to the left hand and fingers They appeared only when some one was watching him, when he was excited, or when he was attempting fine discrete movements with the left hand In association with voluntary movements the predominant involuntary movement was an action tremor

On the fourth post-operative day, he developed clonic convulsive movements of the left side of the face in the morning He was drowsy and uncooperative At 6 30 p.m , similar convulsive movements occurred At 8 00 p.m he had a similar attack but with loss of consciousness salivation, urinary incontinence and tonic followed by clonic muscular contractions of the left leg At one time and for a few minutes only, there was tonic contraction of the entire left upper extremity The entire attack lasted one and one-half hours and ceased following the subcutaneous administration of 120 mgm of sodium phenobarbital and the making of a lumbar puncture Subsequently he was quite alert but temporarily unable to move his left leg Babinski's sign was strongly positive on the left There were no further convulsive seizures At no time was there any aphasia or emotional disturbance No disturbance of the movements of the eyes was ever noted

Facial Weakness

On the first post-operative day the tongue protruded to the left and there was a slight weakness of the lower part of the left side of the face Subsequent movements of the tongue seem to have been normal but the left lower facial weakness persisted for some time, though by October 12, 1940, ten month after the operation it had become so slight as to be hardly perceptible

Left Upper Extremity

Paralysis—Immediately after the operation the left upper extremity was com-

pletely paralyzed Except for the single tonic contraction, it did not even take part in the left-sided convulsions which occurred on the fourth post-operative day No voluntary movements occurred in this extremity until the sixteenth post-operative day, when he was able to flex slightly the left thumb and little finger The following day he was able to flex all of the fingers and to abduct and adduct the thumb slightly On the nineteenth post-operative day he could flex and extend both the elbow and wrist On the twenty-first, he could raise his body while lying prone by extending both arms On the twenty-second, he could abduct the arm at the shoulder and could flex and extend his fingers in unison but not individually On the twenty-third post-operative day he could raise his left hand above his head All movements were gradually increasing in strength and facility By the forty-first post-operative day, practically all movements could be performed with the left upper extremity, although they were slower and more awkward than similar movements on the right Strength of all movements was reduced This was particularly true of extension of the elbow, flexion of the wrist, and extension of the fingers Except for occasional independent extension of the index finger he could not move any finger independently of the others Rapid alternating movements were not possible On the sixty-second post-operative day, strength had improved and some independent movements of the thumb and fingers were possible Ten months after the operation movements at the shoulder were almost the equal of those on the right, except that he could not raise his left arm above his head quite as rapidly or as high as he could the right Flexion and extension of the elbow were free and powerful Pronation and supination of the wrist were as extensive as, though a little slower than, on the right Flexion and extension of the wrist were weak and only about 50 percent as extensive as on the right side Movements of the fingers were much more difficult and slower than on the right He could abduct and adduct the thumb, flex and extend the terminal phalanx of the thumb He could oppose the thumb toward the little finger but could not move the little finger into opposition He cold flex and extend all of the fingers but could move only the index finger independent of all others He could abduct the fingers well but adduction was poor All fine discrete

movements were poorly done However, the strength of his grasp was good Using both hands, he was able to pick up a huge barrel weighing one hundred pounds and set it on a chair When walking, the left arm hung limply at his side and did not swing as much as the right one did

Resistance to Passive Movement—This extremity was completely flaccid immediately after the operation and continued so until the sixteenth post-operative day, when slight resistance to passive movement appeared It never became much, if any, more marked On the forty-first post-operative day and again ten months after the operation, there was no detectable increase in the resistance to passive manipulation of this extremity

Tendon Reflexes—During the first three days after the operation, no tendon reflexes could be elicited in the left arm On the fourth post-operative day, a faint biceps jerk was obtained, but it was not always elicitable thereafter On the tenth post-operative day, Hoffmann's sign became positive On the fourteenth no reflexes could be obtained, but by the nineteenth post-operative day all tendon reflexes, biceps, triceps, and radial jerks, were slightly hyperactive This slight to moderate hyperactivity of the tendon reflexes, including the finger-jerk and Hoffmann's sign on the left side persisted when he was last seen ten months after the operation

Reflex forced grasping was not noted at any time

Left Lower Extremity

Paralysis—He was able to move the left lower extremity freely and powerfully on the day of the operation and thereafter until the severe convulsive seizure at 8 00 p m on the fourth post-operative day Subsequent to this, the left lower extremity was completely paralyzed The following day, however, slight movement was possible On the next, or sixth post-operative day, he could flex and extend the hip and also extend the knee By the ninth post-operative day, all movements were possible On the twelfth he walked with assistance and by the fifteenth post-operative day this extremity seemed almost normal When he was discharged from the hospital, on the forty-first post-operative day, this extremity seemed entirely normal He could hop well on the left foot alone This was true when he was last seen ten months after the operation

Resistance to Passive Movement—During the period of paralysis from the fourth to the fifteenth post-operative days, the left lower extremity was relatively flaccid, otherwise there was at no time any abnormality in the resistance to passive manipulation

Tendon Reflexes—On the first post-operative day the tendon reflexes (knee and ankle jerks) were equal on the two sides On the second post-operative day the left ankle jerk was hyperactive and continued so until the ninth post-operative day when all tendon reflexes in the lower extremities were again equal and continued to be so thereafter.

Babinski's Sign—From the day of operation to the sixth post-operative day this sign was always present on the left On that day it was questionable On the ninth post-operative day it was not present On the tenth and fourteenth day fanning of the little toe was produced but no dorsiflexion of the great toe On the forty-first day, it could be obtained on occasion but ten months after the operation it was definitely absent

Abdominal Reflexes

Prior to the operation these reflexes, though definitely present, were a little less active on the left side Following the operation few observations are recorded but on the forty-first day they could not be obtained on the left side and ten months after the operation they were difficult to obtain on the left side and feeble when elicited

Sensation

Prior to the operation, sensation was intact but light touch (cotton) and pin-prick produced an unpleasant tingling sensation like an electric shock on the left side

Light Touch (Cotton)—On the first post-operative day, he was unable to detect light touch over the left upper extremity The same was true on the next day On the third post-operative day it is noted that there was an almost complete anesthesia to light touch over the left upper extremity and left side of the chest whereas pressure or coarser tactile stimuli were sometimes appreciated but poorly localized. This anesthesia continued until the eleventh post-operative day, when recovery began On the fourteenth post-operative day, there was recorded some diminution

of perception over the left upper extremity and also the left lower extremity but less over the trunk This is the only time that any loss over the lower extremity was noted By the twenty-second post-operative day, this form of sensibility was almost intact It soon became the same as on the right side and continued so

Pain (Pin-Prick)—On the first post-operative day he complained of numbness of the left arm and there was a severe hypalgesia involving the left upper extremity This state, associated with very poor localization, continued until between the eleventh and fourteenth post-operative days when it began to lessen On the fourteenth the threshold for pin-prick was definitely higher over the left arm and leg than over the right, and there was a slight hypalgesia over the left side of the face and trunk. Localization was accurate Thereafter the sensory impairment gradually disappeared Pain sensibility was almost intact on the twenty-second post-operative day On the thirty-third, there was no loss, but pin-prick again had the unpleasant quality which was present before the operation This continued to be the case thereafter

The corneal reflexes were active and equal at all times

Identification of Digits—At no time was there any loss of the ability to identify the proper toe when it was touched But from immediately after the operation until some time after the fourteenth post-operative day he was unable to identify the fingers of the left hand when they were touched or manipulated By the thirty-third day he had regained this ability and maintained it thereafter

Position Sense—At no time was position sense in the toes lost On one occasion, however (tenth post-operative day), one examiner thought it to be somewhat diminished on the left side

Immediately after the operation he was unable, when blindfolded, to find the left upper extremity with the right On the third post-operative day he found his left hand by first finding his left shoulder and then following the arm down to the hand Position sense, as usually tested by passive manipulation, was, of course, totally lost On the fourth post-operative day he had less difficulty finding the left hand but sense of direction of movement at the elbow, wrist, and fingers was still very poor On the fifth he could find his left hand fairly well Position sense had returned to

the elbow but not to the wrist or fingers
On the tenth and fourteenth post-opera-
tive days position sense was again absent
at the elbow, as well as at the wrist and
fingers and diminished at the shoulder
Thereafter recovery progressed rapidly and
these sensibilities were intact on the twenty-
first post-operative day and subsequently

As previously noted, the localization of
points in the left upper extremity which
were stimulated with pin-prick was very
defective for the first two weeks after the
operation

Vibratory Sense—This sensibility was
markedly reduced in the left upper extrem-
ity on the third post-operative day On the
tenth, it was absent in the left upper and
diminished in the left lower extremity By
the twenty-first post-operative day re-
covery was complete.

Stereognosis, etc.—On the eleventh
post-operative day, two-point discrimina-
tion was very defective over the left palm
On the twenty-first post-operative day,
numbers written on the left palm were cor-
rectly recognized about 50 percent of the

time On the thirty-third the recognition
of objects placed in the left hand was good

On the forty-first numbers 1.5 cm high
were correctly recognized when written in
the right palm but for recognition they
had to be 4 to 5 cm high on the left palm
Ten months after the operation the rec-
ognition of objects in the left hand was
good and numbers only 7 to 8 mm high
were correctly recognized when written in
the left palm

Subsequent Note

E S was again seen on April 4, 1913, over
three years after the operation For some
time after the operation he suffered from
convulsions but for many months these had
been completely controlled by adequate
regular doses of phenobarbital For many
months he has been employed in the stock
room of a governmental agency He is still
unable to perform delicate, well co-ordi-
nated movements with the left hand but
can use it for grosser tasks The involuntary
movements are minimal and usually present
only when he is conscious of being observed

Comment on Case 2

As only half of the inexcitable area lying between the "mouth" and the
"finger" areas was removed, it is possible that not quite all of the "arm"
area was removed from the precentral motor cortex. However, it is certain
that more than merely that part of the "arm" area which was electrically
excitable under these circumstances was removed.

In Case 3, too, only the "arm" area was removed, but as in Case 2
some change occurred in the remaining cortex postoperatively. Unlike
Case 2, however, the resulting paralysis of the leg was more persistent, and
this case must be regarded as a removal of the "arm" area with subsequent
additional damage to the "leg" area.

CASE 3

G W S (183906), a man thirty-three
years of age was referred to me by Dr
Orthello R Langworthy of the Johns Hop-
kins Hospital, Baltimore, Maryland

On May 26, 1936, he sustained a severe
cranio-cerebral injury He was unconscious
for a considerable time and states that he
knows nothing of what happened until
three weeks after the accident On recover-
ing consciousness he noted a partial ex-
pressive aphasia and a right hemiparesis

These disturbances improved but were
never completely corrected Seven weeks
after the injury he developed a severe
tremor which involved the right arm and
leg It was present at rest but was most
violent whenever voluntary movements
were attempted It was most severe in the
upper extremity

He was admitted to the University of
Chicago Clinics on September 19 1937, six-
teen months after the injury His speech

was thick, monotonous and poorly articulated At times a minor expressive difficulty was obvious There was a slight weakness of the right orbicularis oculi and a tendency toward overaction of the musculature of the right side of the face on emotional movement All forms of sensation were everywhere intact The tendon reflexes were all hyperactive They were equal in the upper extremities but the knee and ankle jerks were more active on the right side The abdominal reflexes were less active on the right side The cremasteric reflexes were equal Hoffmann's sign could occasionally be elicited on both sides Babinski's sign was present on the right side on occasion Muscular strength was good and bilaterally equal in the four extremities except for slight weakness of the right hand (dynamometer reading—right 115, left 140) and of the extensors and flexors of the right elbow The right thigh and calf were 2 cm and 1 cm smaller, respectively, than the left There was little, if any, difference in the resistance to passive movement in the extremities on the two sides There was a severe tremor involving the right arm and to a less extent, the right leg It was present

at rest (three to four oscillations per second) and greatly increased in intensity on voluntary movement The tremor was absent during sleep

Examination of the blood, urine, and cerebro-spinal fluid revealed no abnormality Roentgenograms of the skull and pneumo-encephalograms appeared essentially normal

Operation

On October 12, 1937 a left osteoplastic flap was reflected, exposing the central area The cortex appeared to be normal except that the subarachnoid space contained more fluid than is usually seen Movements of the right side of the abdominal wall, of the right shoulder, upper arm, forearm, wrist and fingers, right side of the mouth and about the right eye were obtained On one occasion the patient seemed to vocalize as a result of stimulation was lightened as much as possible and the cortex stimulated with a faradic current, using a unipolar electrode (fig 117) The only movement of the lower extremity which was obtained was abduction of the thigh from the uppermost part of the exposed precentral region Movements of the right side of the abdominal wall, of the right shoulder, upper arm, forearm, wrist and fingers, right side of the mouth and about the right eye were obtained On one occasion the patient seemed to vocalize as a result of stimulation
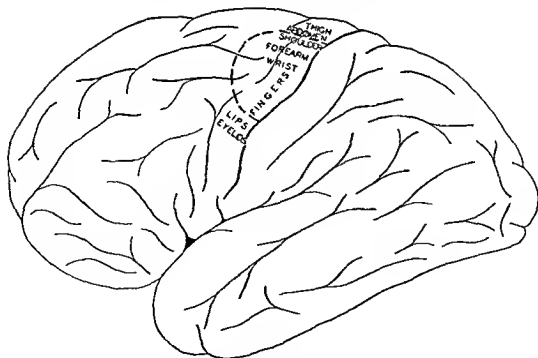
Fig. 117 (Case 3).—Diagrammatic sketch summarizing the results of electrical stimulation and indicating, within the broken line, the area extirpated

tion but this was little more than a grunt The area of representation of these parts of the body was delimited and the area representing the right upper extremity was extirpated (fig 117). The extirpation included the entire anterior wall of the central fissure down to the bottom of the fissure It extended forward including the posterior part of the neighboring frontal convolutions The extirpation included the entire thickness of the cortex and some of the immediately subjacent white matter The defect so produced measured 2.3 by 3.5 cms on the surface It was deepest at the central fissure, 1.5 cms The entire dissection was done with sharp instruments, carefully sparing the "face" area The electrocautery was not used Bleeding was controlled with silver clips

Microscopic Examination

Representative sections were taken from the block of cortex removed The cortex was from areas 4s, 4s, and 6 The absence of a definitely identifiable area 4γ was not necessarily significant as the posterior part of the block was severely traumatized when it was removed The cortex was abnormal There was a considerable reduction in the number of ganglion cells and many of those that remained showed evidence of chronic degeneration

Post-Operative Course

All tremor was immediately abolished and at the last report from Dr Langworthy on June 23, 1941, three years and eight months after the operation it had at no time returned

On the fourth post-operative day the patient developed convulsions localized to the right side of the face In spite of anticonvulsant therapy these persisted for three days and then ceased He made a very satisfactory recovery He was up in a chair on the eleventh post-operative day By the nineteenth day he was able to walk, though with much limping In order that his recovery might be observed he was kept in the hospital much longer than was required by his condition He was discharged to his home in Baltimore on December 20 1937, sixty-nine days after the operation

Aphasia

On the day of the operation there was no definite disturbance but his post-anaes-

thetic state made any detailed examination impossible At 9 00 a m on the first post-operative day (10-13-37) his speech was less well articulated than before operation and by 7 30 p m that day he had a complete expressive aphasia although he could read and apparently comprehend what was said to him On the following (second post-operative) day the expressive aphasia was still complete, and in addition he had become unable to read He still understood and correctly executed simple commands He did not understand when asked to differentiate between the sensation evoked by pin-prick on the two sides of the body and he no longer responded to the command "Put your left fore-finger to your nose," although the left arm was not paralyzed He could not indicate his wants by pointing to the words, "WATER," "FOOD," and "URINAL" printed on a card On the seventh post-operative day (10-19-37) the expressive difficulty was unchanged, but he became able to indicate his wants by pointing to words printed on a card On the tenth post-operative day he laughed at a joke about his long whiskers but was still unable to speak He was shown a spoon, a key, a pen, a knife, a ruler, a light bulb, a battery, a pad of paper, and a paper on which the following questions were written What do you do with each article? (1) eat with, (2) open a door, (3) write a letter, (4) cut (5) measure, (6) light a room, (7) put in a flashlight, (8) write upon He correctly associated each article with the proper question On the afternoon of the ninth post-operative day, he printed on a piece of paper with his left hand, "Give me nice [nurse?] company up here" He was moved into the ward and seemed grateful On the eleventh post-operative day (10-23-37) he spoke for the first time after the onset of the aphasia and by the following day his speech was almost as fluent as before the operation His vocabulary gradually increased and his speech has soon comparable to that present before operation There had always been some slurring ever since the original accident

Facial Weakness

A slight weakness of the lower part of the right side of the face about the mouth was present on the day of operation (10-12-37), and by the second post-operative day (10-14-37) there was a severe paralysis involving all parts of the face On the fol-

lowing day it was less marked In spite of the facial convulsions which were present from the fourth through the sixth post-operative days, the weakness was much less severe on the seventh post-operative day and present only with voluntary grimacing and not when laughing By the eleventh day (10-23-37) it was almost gone Thereafter only a very slight right facial weakness persisted, which was still present when he was discharged, sixty-nine days after the operation On June 23, 1941 three years and eight months after operation, Dr Longworthy reported "The cranial nerves are normal except that emotional responses are more marked on the left side of the face"

Eye Movements

On the day following the operation there was slight weakness of conjugate movements of the eyes to the right This paralysis was practically complete the following day By the seventh day there was only moderate limitation of deviation of the eyes to the right Thereafter all movements of the eyes rapidly returned to normal and have remained so

Right Upper Extremity

Paralysis—There was a complete paralysis of the right upper extremity which was present immediately after operation and continued, except for involuntary associated movements, as will be noted below, until the thirteenth post-operative day, when a feeble flexion of the fingers appeared On the sixteenth post-operative day (10-28-37) he could extend the wrist slightly On the eighteenth he could flex the fingers slowly and completely when done synchronously with a similar movement on the left side However, he could readily close the left fist without moving the right He could not extend the fingers of the right hand He could flex the right elbow feebly but not extend it Though the pectoral muscles could be seen to contract, there was no movement at the right shoulder joint On the twenty-first post-operative day (11-2-37) he could flex the elbow against gravity, extend the wrist weakly but not flex it, could flex all the fingers and the thumb, but only in unison There was a slight forward movement of the right shoulder and very slight abduction of the arm at the shoulder On the twenty-sixth post-operative day, he could abduct

the arm at the shoulder, and very weak extension of the fingers was observed By the thirty-first post-operative day flexion of all the fingers together had become quite forceful On the thirty-fourth post-operative day (11-15-37) slight extension at the elbow became possible By the thirty-seventh post-operative day, he could abduct the arm well at the shoulder and flex the wrist On the fortieth post-operative day, he could raise the right hand up to the left shoulder Flexion and extension of the wrist and fingers were improving On the forty-fifth he could place the right hand on top of his head On the fifty-ninth, flexion and extension of the elbow was stronger The right shoulder drooped as he walked On the sixty-sixth post-operative day (12-17-37), just prior to his being discharged, it was noted that there had been continuous improvement in the voluntary control of the right upper extremity, but well co-ordinated movements were difficult or impossible Independent movements of individual muscles or small groups of muscles, particularly in the hand, were very defective All of the fingers continued to move only together He was unable to elevate the right shoulder He could abduct the arm at the shoulder forty-five degrees and could move the arm backward and forward at the shoulder by the same amount He could flex and extend the elbow fully and pronate the wrist fully, but supination was limited to forty-five degrees He could flex the wrist twenty degrees and extend it ten degrees He could flex and extend all of the digits fully, but he could not move any one independently of the other four However, he could flex and oppose the thumb and index finger while moving the others but little He could not hold a pencil or button his clothes with the right hand He could hold a glass and lift it to his lips Four months after the operation, Dr L C Kulb of Baltimore estimated the strength of the right upper extremity as 60 percent of that of the left Two years and eight months after the operation (June 1940), Dr Kolb stated that he had full range of voluntary movement at the shoulder and elbow He was unable to execute any fine isolated movements of the fingers All movements on the right side were weaker than on the left Three years and eight months after the operation, Dr Langworthy wrote "with effort he can raise the right arm well above his head He moves

the arm at the elbow freely. There is little power of movement at the wrist and almost none of the fingers He is able to dress himself except for fastening the left cuff"

Involuntary Associated Movements— On the first post-operative day it was noted that when he yawned the fingers of the right hand flexed forcefully This was never again observed On the eleventh post-operative day and repeatedly thereafter, the right arm, wrist and fingers would be extended and lifted off the bed when he yawned At no time following the operation did the right arm swing normally as he walked, rather it hung loosely at his side and flopped as he walked

Resistance to Passive Movement—On the day of the operation there was definite spasticity of the extensor muscles of the arm but not of the flexors On the following day, the fingers and wrist were flaccid but spasticity was present in both the flexor and extensor muscles at the elbow On the second post-operative day, there was mild resistance to passive movement in the flexors and extensors of the wrist, moderate resistance in the pronators of the forearm and in the flexors and extensors of the elbow There was marked spasticity in the adductors of the arm at the shoulder but none in the abductors On the following day the spasticity was of the same distribution but seemed less marked On the sixth day the spasticity of the flexors and extensors of the elbow continued, and the musculature of the fingers was still flaccid On the eleventh post-operative day the condition was considered as unchanged or a little more marked On the eighteenth day typical clasp-knife spasticity in the flexors and extensors of the elbow and flexors of the wrist was recorded There was no resistance in the extensors of the wrist With the wrist held extended, there was slight resistance in the flexors of the fingers, whereas with the wrist flexed, there was slight resistance in the extensors of the fingers but none in the flexors On the twenty-first day (11-2-37), there was no resistance to passive movement at the shoulder but typical clasp-knife spasticity in the flexors and extensors of the elbow On the sixty-sixth day, the condition was largely unchanged except that the resistance in the flexors of the wrist and fingers was more marked As he stood or walked the arm hung loosely and vertically at his side there being no posturing other than

that imposed by gravity, except that the fingers were semi-flexed Two years and eight months after the operation, Dr Kolb noted increased tone in the flexors at the elbow, wrist, and fingers Three years and eight months after the operation (June, 1941) Dr Langworthy stated 'The arm hangs at the side in full extension There is little spasticity of the muscles around the shoulder girdle or elbow There is spasticity of the flexor muscles of the wrist and fingers"

Tendon Reflexes—On the day of operation the tendon reflexes (biceps, triceps, and radial jerks) were all hyperactive on the right side, as compared with the left The following day Hoffmann's sign, which apparently was not sought on the day of operation, was strongly positive on the right side and clonus could be elicited on sudden supination of the hand With slight variations from time to time, this hyperactivity continued but gradually diminished somewhat At two years and eight months, Dr Kolb reported that the tendon reflexes were still hyperactive on the right, that Hoffmann's sign and clonus at the wrist could still be elicited At three years and eight months, Dr Langworthy found the wrist clonus still present

Reflex Grasping—On the day of operation reflex forced grasping was mildly present in the right hand It was more marked the following day On the sixth post-operative day it could not be elicited and was never observed thereafter

Atrophy—Prior to the operation, measurement revealed no difference in the circumference of the upper arms and forearms During the sixty-nine days that he remained under our observation in Chicago, no atrophy was observed but actual measurements were not recorded post-operatively In June, 1940, two years and eight months after the operation, Dr Kolb found the right forearm to be 2 cm smaller in circumference than the left and the right upper arm to be 1 cm smaller In June, 1941, Dr Langworthy reported that the right arm was definitely smaller than the left

Right Lower Extremity

Paralysis—On the day of operation he could move the thigh and leg slightly, but the foot and toes were completely paralyzed On the following morning, at 9 00

a.m., he could also move the foot at the ankle slightly, but the toes were still paralyzed. At 7 30 p.m., that same day, the entire right lower extremity was paralyzed. This continued until the sixth post-operative day, when slight movement of the thigh and hip returned. There was no further change until the sixteenth post-operative day when he was able to move his toes up and down. Thereafter improvement continued steadily, and by the eighteenth day movement was possible at all joints in the right lower extremity. Extension at the knee was very forceful, while dorsi-flexion of the foot was very weak. On the nineteenth post-operative day (10-31-37), he walked with much limping, and on the twenty-sixth he walked unassisted but with a typical hemiparetic gait. Good voluntary movement of the foot was noted on that day. By the forty-eighth post-operative day (11-29-37) he was able to lift the foot clear of the floor as he walked, although there was still a moderate amount of circumduction. On the sixty-sixth day he limped slightly on the right leg and did not lift the right foot as high as the left. All voluntary movements were possible and of normal range in the right lower extremity, although they were all somewhat weaker than on the left side. At two years and eight months, Dr Kolb reported that he walked with circumduction of the right leg. In June 1941, Dr Langworthy stated 'The leg is circumducted in walking. Dorsi-flexion of the ankle is weakest in the right lower extremity'.

Resistance to Passive Movement—On the day of operation there was extensor spasticity in the right lower extremity though it was less marked than in the arm. The following day the limb was described as mildly spastic. On the second post-operative day there was moderate resistance in the extensors of the hip and knee but none in the flexors. There was marked resistance to dorsi-flexion of the ankle with clonus. Thereafter the spasticity increased slightly until during the second week post-operatively and then gradually diminished. When he was discharged (66th post-operative day), there was no detectable increase in the resistance to passive movement in the right lower extremity, as compared with the left. However, at two years and eight months Dr Kolb reported some hypertonus in the extensor muscles, and a year later Dr Langworthy said, "There is little

spasticity in the right leg but ankle clonus is present."

Tendon Reflexes—Immediately after the operation the tendon reflexes (knee and ankle jerks) were hyperactive in the right lower extremity, and both ankle and patellar clonus could be elicited. The following day the same was true, except that the patellar clonus had disappeared. It returned subsequently, however. On the seventh post-operative day, Rossolimo's sign was not present, but when he was discharged it as well as the Mendel-Bechterew's sign, was readily elicited on the right. The knee and ankle jerks were still hyperactive on the right and an unsustained patellar and a sustained ankle clonus were present. At four months, Dr Kolb reported that the tendon reflexes were slightly more active on the right and at two years and eight months that they were hyperactive and clonus could be elicited at the right ankle. At three years and eight months, Dr Langworthy found that the deep reflexes in the legs to be overly active bilaterally," and clonus could still be elicited at the right ankle.

Babinski's Sign—Babinski's sign was present on the right side immediately after the operation and continued so throughout his stay in Chicago. At four months Dr Kolb was uncertain as to its presence bilaterally. At two years and eight months, he reported it to be present on the right side. However, in June, 1940 Dr Langworthy found it to be absent.

Atrophy—Prior to the operation the right thigh was 2.0 cm smaller in circumference than the left, and the right calf was 1.1 cm smaller. Two years and eight months after the operation the right thigh was 3.5 cm smaller and the right calf was 3.0 cm smaller. In June, 1941 Dr Langworthy commented on the obvious atrophy of the right leg.

Abdominal Reflexes

On the seventh post-operative day, the abdominal and cremasteric reflexes were absent on the right side. They had, however, returned and were active on the sixth-sixth post-operative day.

Vasomotor Changes

My associate, Dr William H. Sweet, made careful and repeated studies of the cutaneous temperatures of various parts of the

body in this case, both before and after the operation His findings are summarized in Table V

In addition, it was noted during the latter part of this patient's stay in the hospital that when the right arm hung down for very long it became red, warm, and moist, and on palpation the right hand was distinctly warmer than the left However, in April, 1935, about six months after the operation, the patient reported that his hand was cold and blue Neither Dr. Kolb nor Dr Langworthy commented upon any changes of this nature

Sensation

The recorded observations on sensation are by no means as full as they should be This is partly due to the facts that on the day of operation his post-anaesthetic state precluded satisfactory sensory examination, and that from the latter part of the next day until the twelfth post-operative day, the severe aphasia made reliable sensory examination impossible

Perception of light touch (cotton) was definitely diminished over the right extremities but not over the trunk on the first post-operative day (10-13-37) When he was discharged (66th post-operative day) this form of sensibility was intact, except that stroking the sole of the foot caused a tickling sensation only on the left side

Examination with pin-prick was never satisfactory during the early post-operative days. Later this form of sensation was intact.

On the first post-operative day, vibration of a tuning fork was perceived everywhere but less acutely over the entire right side At time of discharge there was no disturbance of this form of sensibility

Sense of movement and of position were absent in the right fingers, at the right elbow, and wrist on the first post-operative day Movement at the shoulder was correctly interpreted He was unable to find his right hand with his left, when he was blindfolded This form of sensation at this time (first post-operative day) was intact in the lower extremities When he left the

Table V
DIFFERENCES IN SURFACE (SKIN) TEMPERATURES ON THE TWO SIDES OF THE BODY*

	Pre-operative Temperatures		Post-operative Temperatures			
	October 11		October 12	October 13		November 7
			5 p m	7 30 a m	5 p m	
Room temperature	24 4C	16 6C	24 6C	23 9C	16 6C	20 5C.
Forearm	0	+0 6	−0 3	−0 4	+0 5	−0 1
Dorsum of hand	−0 1	+0 3	−0 9	−0 2	+0 6	+0 5
Palm	−0 7	+0 3	0	−0 1	+0 9	−1 0
Thumb	+0 4	0	−1 5	−0 1	0	0
Middle finger	+0 3	0	−1 9	+0 2	+0 6	0
Little finger	+0 2	−0 1	−0 5	0	+1 3	+0 8
Leg	−0 5	−0 1	+0 1	+0 1	+0 5	−0 7
Dorsum of foot	+0 4	+0 1	+0 1	+0 1	+0 2	0
Sole	+0 1	+0 3	+0 3	−0 3	+0 3	0
Large toe	+0 5	0	+0 5	+0 1	+0 7	+0 2
Middle toe	+0 1	−0 1	+0 2	−0 05	+1 7	−0 4
Little toe	+0 6	+0 8	+0 7	+0 5	+1 7	0

* The figures recorded in the table indicate the difference between the surface temperatures on the right side of the body and those on the left Thus, +0 5 indicates that a given point on the right extremity was 0 5 degree C (0 9 degree F) warmer than the same point on the left

hospital in Chicago, and at all subsequent examinations, position sense was intact in all extremities

On the first post-operative day he was unable to recognize articles or textures with his right hand and unable to identify numbers written in the right palm though he

did identify them when they were written on the right forearm, upper arm, and chest. Two-point discrimination was increased to 1 cm on the right finger tips Similar disturbances of sensation were never found again, though they were carefully looked for on the sixty-sixth day

Comment on Case 3

Several points are of particular interest here. Unlike the other cases, the immediate post-operative paralysis was not flaccid but spastic. In previously discussing this case (Bucy and Case, 1939). I have said that this immediate appearance of spasticity is probably to be attributed to the severe cerebral injury 16 months prior to the operation which resulted in a temporary aphasia and right hemiplegia It will also be recalled that even prior to the operation the tendon reflexes were more active in the right leg.

The observations relative to the alterations in temperature of the skin are also more complete here than in the other cases and indicate a very temporary disturbance of the vasomotor mechanism similar to that seen by Kennard (1935) in subhuman primates and that reported by me (1935) in an individual with a capsular hemiplegia of sudden onset.

In Case 4 the representation of the arm, trunk, and leg was removed from the precentral cortex, resulting in the most profound change present in any case of this series.

CASE 4

C M L (233566), male, 31 years of age Referred by Dr J B Rayman, of Toledo, Ohio. He was admitted to the University of Chicago Clinics on December 28, 1939, and discharged on February 26, 1940

About 1930 he first noted an occasional fine tremor of the fingers of the left hand This gradually developed into a typical parkinsonian tremor, involving the left side of the body It became very severe in the upper extremity and mild in the face and lower extremity It had shown no progression for four years It was present during all of his waking hours, except when abolished by drinking alcoholic beverages He also experienced attacks in which his eyes would turn upward The Wassermann test on the blood was found to be positive in 1928 He subsequently received intensive anti-luetic treatment

Examination

The tremor was a typical parkinsonian tremor, present at rest. There was a definite mask-like facies with a mild left lower

facial weakness He was unable to shrug his left shoulder but otherwise strength in the left upper extremity was good However, the tremor, and to a lesser extent, the slowness and rigidity (cog-wheel type) made useful movements of the extremity impossible On walking the left arm did not swing and he limped a little on the left leg. Otherwise the lower extremity was strong The tendon reflexes on the left side were all hyperactive The abdominal reflexes were active Babinski's sign was present on the left but Hoffmann's sign was not The left trapezius muscle was not only weak but somewhat atrophied, and there was definite atrophy of the muscles of the left hand, left forearm and upper arm and of the deltoid muscle Unfortunately, no measurements were made Sensation was intact in all modalities

It was demonstrated that the drinking of ethyl alcohol (360 cc, 45 percent) sufficient to produce 222 mgm percent of alcohol in the blood abolished the tremor temporarily and also induced greater weakness in the left arm and leg.

Laboratory Tests

The urinalysis and blood count were normal The Wassermann and Kahn tests on the blood were negative The spinal fluid was normal except for a mildly positive Wassermann (1-1-0-0 0) Ordinary X-ray pictures of the skull and a pneumoencephalogram were normal An electroencephalogram was normal, except that there was an unusual number of waves of the type commonly associated with sleep, and on one occasion a rhythmic discharge was recorded from the *right* central region at 5 per second synchronous with the left-sided tremor At the same time no comparable discharge could be obtained from the left side Similar discharge was never obtained again Electromyograms showing an electrical disturbance in the muscles of the forearm, synchronous with the tremor were obtained Neither the tremor nor this electrical discharge was present after the operation

Operation

On January 11, 1910, under light ether anesthesia, an osteoplastic flap was reflected, exposing the right central region up to the sagittal fissure The arachnoid membrane was somewhat milky and the subarachnoid space contained more fluid than usual Except for these minor alterations the exposed surface of the brain appeared normal

With a 60-cycle sinusoidal electric current at 4 to 6 volts applied with a bipolar electrode, the entire exposed cerebral cortex was stimulated Responses, all on the left side of the body, were elicited only by stimulation of the posterior part of the precentral gyrus The uppermost part of the gyrus was covered by a tangle of veins making stimulation difficult From this region, flexion of the hip was elicited Further downward, movements of the shoulder, elbow, wrist, and fingers, in that order, were elicited Below this region, in the lowermost part of the precentral gyrus, which was exposed, stimulation produced rotation of both eyes to the left

A block of cerebral cortex extending from the depth of the rolandic fissure forward to include the posterior part of the first and second frontal convolutions and from the interhemispheric fissure downward to just above the point from which eye-movements were elicited was removed (fig 118) The tissue removed included all of the cortex and the immediately subjacent white matter The central veins emptying into the superior longitudinal sinus were preserved except for one large vein which lay just anterior to the rolandic fissure parallel to it The extirpation also included the tissue of the uppermost gyrus
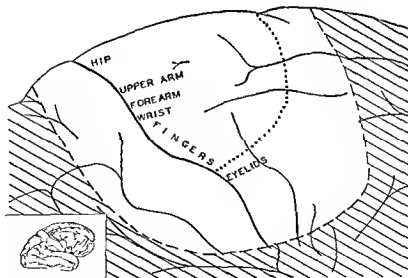
Fig 118 (Case 4) —Diagrammatic sketch of the field exposed at operation, summarizing the results of electrical stimulation and indicating, within the dotted line, the area extirpated

on the medial surface of the hemisphere
The cavity produced measured 3.25 cm
along the interhemispheric fissure, 4 cm
along the rolandic fissure, 2 cm along the
inferior margin, and 2.5 cm along the an-
terior margin It was 2.5 cm deep along the
rolandic fissure but the floor sloped upward,
making it less deep anteriorly

It was thought that the entire representa-
tion of the upper and lower extremities in
areas 4 and 6 of the right cerebral hemi-
sphere had been removed

Microscopic Examination

The piece of cerebral cortex which was
removed was cut into nine blocks, and
representative sections were cut from each
and stained with thionin For the most part,
the cortex was typical of the agranular pre-
central cortex ie areas 4a, 4s and 6
Anteriorly a little granular prefrontal cor-
tex was visible and posteriorly a few Betz
cells were seen That more of area 4γ is
not present in these sections is not surpris-
ing in view of the fact that the posterior
part of the block was removed subpially
mutilating this region considerably The
cortex appeared relatively normal There
was no evidence of inflammation or of vas-
cular occlusion There was possibly some
reduction in the number of cells, particu-
larly in layer III and in some sections
many of the cells which remained seemed
unduly pale, but these changes were not
striking

Post-Operative Course

The tremor was completely abolished, ex-
cept for a fine tremor of the jaw and face
and has remained so to date, January, 1943
He was able to be up in a wheel-chair on
the fourth post-operative day He walked
without assistance on the seventeenth day
after operation His recovery was rapid
and without incident, but he remained in
the hospital until February 26 1940, forty-
six days after the operation in order that
we might observe the course of his re-
covery Since then he has been seen on
several occasions and has written numerous
letters in which he has intelligently de-
scribed his condition in detail At present
over three years after the operation, he is
employed in the stock room of a large
industrial plant

Emotional Change

Shortly after the operation it was obvious
that he was definitely un-stable emotionally

He would weep on the slightest provoca-
tion and in response to unusual stimuli,
such as hearing the beauty of an auto-
mobile described over the radio He said
that this was uncontrollable and not as-
sociated with any feeling of sadness In fact,
he often actually felt happy when he cried
He attributed this condition to being over-
joyed with the freedom from the tremor
At no time was there any similar uncon-
trolled outburst of laughing This state con-
tinued unchanged for about two weeks,
when it began to diminish in severity By
the twenty-ninth post-operative day he was
still inclined occasionally to cry uncon-
trollably but thereafter this state rapidly
disappeared

Eye Movements

Prior to the operation he occasionally
suffered from oculogyric spasms in which
the eyes would turn upward None of these
occurred during the month and a half that
he remained under our continuous observa-
tion after the operation but eight months
after the operation he informed us that
very rarely he suffered from attacks in
which the eyes would involuntarily turn
to the right These were most apt to occur
when he was excited or after drinking about
four bottles of beer

On January 31 1941, a year after the
operation, and on April 2 1941 fifteen
months after the operation, he stated that
the eyes never rolled upward as they did
before the operation but on occasion, as
when watching bowlers watching pool balls,
playing cards or after drinking beer the
eyes seemed to be drawn to the right
never to the left However his friends tell
him that there is no actual movement of
the eyes

There are no notes relative to any dis-
turbances of movements of the eyes until
the eighth post-operative day when it was
noted that voluntary conjugate movement
of the eyes either upward or to the left was
slow and difficult This had disappeared by
the twenty-ninth post-operative day, the
only remaining trace being a few nystag-
moid jerks on looking to the extreme left
Even these soon disappeared

Facial Weakness

A slight weakness of the lower part of
the left side of the face was present im-
mediately after the operation It began to
diminish two weeks after the operation but
never completely disappeared He experi-

enced difficulty in winking the left eye alone On April 2, 1941, fifteen months after the operation there was still a slight weakness of the entire left side of the face, though it was not marked about the mouth This, however, was present before the operation.

Left Upper Extremity

Paralysis—Immediately after the operation there was a complete paralysis of the left upper extremity This persisted unchanged until the eighth post-operative day when, on one occasion, feeble flexion of the elbow was observed No further movement was noted until the eleventh post-operative day when he was able to abduct the arm an it the shoulder moving the elbow a distance of six inches He could also flex the forearm against gravity from complete extension to a right angle. On the twelfth post-operative day he could pronate the hand Thereafter strength progressively increased and more movements returned On the seventeenth post-operative day he could extend as well as flex the elbow and he could flex the fingers weakly Improvement continued and by the forty-fourth day he could abduct the arm at the shoulder against gravity through an angle of 75 degrees Adduction was fairly strong He could flex the elbow through 120 degrees against gravity Extension of the elbow was fairly strong He could pronate the hand but not supinate it He could extend the wrist through an angle of 30 degrees against gravity but he could not flex it He could flex all of his fingers into the palm but not move any one of them independently of the others Extension, abduction, and adduction of the fingers were not possible On the eighty-second post-operative day, the strength of all movements was increased, and he could flex the wrist but not extend it Extension of the fingers and supination of the wrist were practically absent Eight months after the operation he was able to raise the left hand up to his head Movement at the elbow, both flexion and extension was fairly strong The grasp was good Extension of the wrist and fingers was very weak He could not move individual fingers He did not use the left hand except for such simple tasks as holding a package of cigarettes while he opened it

On April 2, 1941, fifteen months after the operation he could raise the left hand over his head He had noted that movement was

freer on arising in the morning than it was later in the day Elevation of the left shoulder (shrugging) was very weak but movements at the shoulder joint (abduction, internal and external rotation) were all strong except that abduction was not as forceful as on the right Flexion and extension of the elbow were strong Pronation and supination of the wrist were very weak. Extension of the wrist was weak and flexion absent Flexion of the fingers was weak, while extension, abduction, and adduction of all fingers and opposition of the thumb against the little finger were absent Flexion of the thumb was the only independent movement of any digit that he could make This condition has shown little, if any, change since then

Resistance to Passive Movement—On the first post-operative day the left upper extremity was flaccid, except that on extension of the elbow there was a definite catch when the forearm formed an angle of approximately 150 degrees with the upper arm As extension was continued this gave way quickly and there was no further resistance This flaccid state persisted until the eighth post-operative day when slight resistance to passive stretching of the flexors of the elbow and wrist and of the pronators of the forearm appeared There was no resistance to stretching of the extensors of the elbow, wrist, or fingers, of the supinators of the forearm, or of the flexors of the fingers The amount of resistance gradually increased On the eleventh post-operative day some resistance was first detected in the flexors of the fingers On the seventeenth post-operative day, when he began to walk without assistance, the left arm hung flaccid at this side On the forty-fourth post-operative day, just before he left the hospital, the left arm still hung dependent with no posture other than that imposed by gravity When he was sitting the arm was usually held with the elbow and fingers semiflexed On passive manipulation there was slight resistance in the adductors of the arm at the shoulder a typical clasp-knife resistance in the flexors of the elbow and a similar, though less marked, resistance in the extensors of the elbow There was spasticity of the flexors but no resistance to passive stretching of the extensors of the wrist and fingers Clonus could at times be elicited by sudden stretching of the pronators of the forearm On the eighty-second post-operative

day and eight months after the operation a moderate spasticity of the distribution described above was present On April 2, 1941, fifteen months after the operation, there was clasp-knife spasticity in the adductor muscles as well as the internal and external rotators but none in the abductors of the left shoulder There was similar spasticity in the flexors but none in the extensors of the elbow, wrist, and fingers, and in the pronators, but not in the supinators, of the wrist A sustained clonus could be elicited by suddenly stretching the flexor muscles of the left wrist or fingers When walking the arm hung straight down unless he became excited, and then it flexed slightly at the elbow, wrist, and fingers

Tendon Reflexes — On the first post-operative day the biceps, triceps, and radial jerks were all hyperactive on the left side but Hoffmann's sign could not be elicited This hyper-reflexia continued Hoffmann's sign was positive fourteen days after the operation and continued so thereafter As previously noted, conus could at times be elicited by suddenly stretching the pronators of the wrist Eight months after the operation conus could be readily elicited in the flexors of the wrist, all tendon reflexes were still hyperactive, and Hoffmann's sign was present. Fifteen months after the operation the left biceps and radial jerks were very hyperactive, but the triceps jerk was not increased, being equal to that on the right side Hoffmann's sign was still readily elicited on the left side Reflex forced grasping was never elicited

Associated Movements — At no time, either before or after the operation, did the left arm swing when he walked as the right one did While in the hospital no involuntary movements associated with yawning or any emotional stimuli were noted, but on March 10, 1940, two months after the operation, he wrote that the arm flexed at the elbow when he yawned This phenomenon continued, and fifteen months after the operation he stated that when he yawned or heard a loud noise the left elbow would flex to a right angle and the fingers would close into his palm.

On April 9, 1940, three months after the operation, he noted that when he met old friends while out walking or when he walked in front of a crowd the left arm would become extended and then be abducted from the shoulder about a foot (about 15 degrees)

On June 1, 1940, five months after the operation, he reported that when he stretched his arms in the morning the fingers on the left became extended "as stiff as a board" and sometimes were even bent backward

On July 1, 1940, about six months after the operation, he reported that at the height of sexual orgasm the left arm would, with a jerk, be extended and adducted against his side It would as quickly relax On July 29, 1940, he reported that an automobile came up behind him quietly and unexpectedly When he turned and saw it he was startled and "my left arm flew up in one jerk completely over my head." It relaxed in a few seconds Eight months after the operation involuntary associated movements similar to those described above were still present He had also noted that when he is alone or not conscious of being watched he walks freely and the left arm, hanging dependent, swings slightly But when he is observed or is on a crowded street, the left arm flexes slightly, does not swing, and his left leg stiffens, making his hemiparetic gait more obvious On September 30, 1940, eight and one-half months after the operation, he also reported that "when I get the least bit chilled my leg gets stiff and it is more difficult for me to walk."

On January 31, 1941, just over a year after the operation, he expressed the opinion that the tendency for his arm to be involuntarily lifted up and away from his body when in the presence of people was gradually decreasing However, it is still present (January, 1943).

Left Lower Extremity

Paralysis — On the first post-operative day the left lower extremity was completely paralyzed except for very weak extension of the knee This state continued until the sixth post-operative day when feeble flexion of the knee became possible On the eleventh post-operative day some forceful extension of the knee, as well as feeble flexion, was possible There was also slight internal rotation of the thigh but no movement of the foot or toes Two days later, the thirteenth post-operative day, external rotation of the thigh was possible, flexion of the knee was more forceful, and he could raise the extended leg two feet off the bed by flexion of the thigh On the seventeenth post-operative day all movements previ-

ously present were stronger He could extend as well as flex the thigh Adduction of the thigh was moderately strong but abduction was weak On this day strong plantar-extension of the foot On this day for the first time since the operation he walked without assistance In doing so he scraped the toes on the floor By the twenty-fifth post-operative day he was able to dorsi-flex and plantar-extend the foot On the thirty-fifth he was able to walk easily. The left leg was circumducted and the toes and anterolateral part of the foot scraped the floor a little. On the forty-fourth his walking was improved He could even walk tandem, i.e , heel to toe, although awkwardly He could not hop on the left foot alone. Flexion of the left hip, abduction and adduction of the thigh, and extension of the knee were all strong Extension of the hip, flexion of the knee, and plantar-extension of the foot were all weak There was no movement of the toes or dorsi-flexion of the foot On the eighty-second post-operative day flexion of the knee and plantar-extension of the foot had become fairly strong The peroneal muscles and dorsi-flexors of the foot were powerless At eight months the condition was the same, except that he stated that when lying down, relaxed, he was often able to move his toes Fifteen months after the operation all movements on the left side were weaker than those on the right However, extension of the knee was but little reduced as compared with the right side Flexion, extension, abduction, and adduction at the hip and flexion of the knee were strong Internal and external rotation of the thigh at the hip were moderately strong Dorsi-flexion and plantar-extension of the ankle were weak Dorsi-flexion of the toes was very weak and plantar-flexion, absent

On walking he circumducted the left leg slightly. He was unable to hop on the left foot alone but he could walk tandem well

Resistance to Passive Movement—The left lower extremity showed no resistance to passive manipulation until the fifteenth post-operative day when for the first time after the operation slight clasp-knife resistance was encountered upon stretching the extensors of the knee. This gradually increased and extended until just before he was discharged, on the forty-fourth post-operative day, there was slight resistance in the adductors and flexors of the hip, definite though not marked clasp-knife resist-

ance in the extensors of the knee, and some mild resistance in the plantar-extensors of the foot There was no resistance in the flexors of the knee or dorsi-flexors of the foot. On the eighty-second post-operative day, at eight months, and at fifteen months after the operation there was moderate spasticity of similar distribution

Tendon Reflexes— On the first post-operative day the knee and ankle jerks on the left were hyperactive, and a sustained ankle clonus could be readily elicited This condition did not change subsequently At no time could patellar clonus be elicited

Babinski's Sign— Plantar stimulation evoked dorsi-flexion of the left great toe and fanning of the other toes on the first post-operative day and at all subsequent examinations But Babinski's sign was present before the operation

Abdominal Reflexes

On the first post-operative day the abdominal reflexes on the left side were present but weaker than those on the right This state persisted until the forty-fourth post-operative day when they were active and equal on both sides and have been so ever since

Atrophy

As no measurements were made prior to operation, it is not possible to compare the degree of atrophy before and after this cortical excision But on the forty-fourth post-operative day, the right forearm measured 29 1 cm in circumference the left 25 8 cm Similar differences of 2.5 to 5 cm between the right and left upper and lower extremities were present fifteen months after the operation, but some atrophy was present on the left side prior to the operation

Sensation

Light Touch (Cotton)— There was no disturbance of this form of sensation at any time post-operatively.

Pain— There was no disturbance of pain (pin-prick) sensibility except for a slight hypalgesia over the left side of the face and slight diminution of the left corneal reflex from the eighth to the eleventh post-operative days

Identification of Digits— On the first post-operative day he was unable to iden-

tify his fingers when they were touched but was able to identify his toes. On the third post-operative day he had some difficulty in identifying his toes but this soon disappeared. The difficulty in identifying his fingers had disappeared by the fifteenth post-operative day and was never again present.

Stereognosis, etc. — On the first post-operative day he had great difficulty in recognizing numbers written in the palm of the left hand. On the eighth post-operative day he could recognize no numbers written in his hand and only about 50 per cent of the objects placed in his left hand. By the eleventh post-operative day he could recognize about 50 per cent of the numbers as well as the objects. On the fifteenth the recognition of all figures was accurate. There was still some difficulty in recognizing objects but this soon disappeared.

Position Sense — On the first post-operative day he had marked difficulty in finding his left hand when his eyes were closed, and position sense in his fingers was absent but was intact in the toes. On the eighth post-operative day the same was true. More extensive testing revealed that position sense was also abolished at the left wrist and elbow but was intact at the shoulder. On the eleventh day he was aware of passive movement at the left shoulder, elbow, wrist, and fingers, but of the direction of the movement only at the shoulder and elbow. Position sense was accurate in the lower extremity, but the responses were somewhat more slowly given than those to movement on the right side. By the fifteenth, position sense was much improved in the fingers though not as good as on the right. It was entirely restored by the thirty-fifth post-operative day.

Vibration Sense — Vibration sense was never reduced or lost but on the first post-operative day this sensation was said to be more intense on the left side of the body.

Comment on Case 4

There are several points of especial interest in this case. In contrast with Case 1, in which only part of the "leg" area was removed, and with Case 2, in which only the "arm" area was removed, the amount of paralysis was considerably greater in both the upper and lower extremities. But the paralysis was not as severe as that seen in many cases of capsular hemiplegia or as that reported by Dandy and by Gardner when much of the cortex of one hemisphere, including all of the precentral motor cortex was removed—and furthermore, although definite spasticity developed, it was not as severe as is commonly seen with a capsular hemiplegia.

It is of considerable interest to note that although the entire representation of the trunk lying between the "arm" and "leg" areas was removed, the abdominal reflexes, although initially somewhat depressed were never abolished and eventually returned to their normal vigor.

Summary of Clinical Observations

In considering the observations made here it should be constantly borne in mind that the extirpations were not limited to area 4 or area 6 or to any subdivision of either of these areas; and that the extent and location of the extirpation or of additional damage done at the operation could not in any case be confirmed by postmortem examination of the brain as all of these patients still survive.

Electrical Excitability—No effort was made to study the problem of electrical excitability in detail in these cases, and for a complete consideration of this aspect the reader is referred to Chapter XIII. In the main, my observations are in agreement with those of Foerster and of Penfield One point is worthy of further comment. In these cases, as well as in others not reported here (Bucy, 1940), stimulation of the uppermost part of the precentral gyrus on the lateral surface of the hemisphere commonly evoked movement of the contralateral extremity at the hip. In those instances where such results were not obtained (Case 2), this uppermost part of the precentral gyrus was not excitable. In no case did the representation of the upper extremity extend all the way up to the interhemispheric fissure Rarely does stimulation of the lateral surface of the hemisphere evoke movement at the knee or ankle or of the toes

In another patient (P de F) operated upon on August 3, 1943, I was able to confirm in man some of the observations on the suppressor strip (area 4s) made by Hines (cf. Chapter XVIII) in the monkey and by McCulloch (cf. Chapter VIII) in the monkey and other subhuman primates (Bucy and Garol, 1944). By stimulation of the anterior lip of the superior precentral sulcus just ventral to the superior frontal sulcus, the resistance to passive manipulation produced by lightening the ether anaesthesia could be abolished in the contralateral upper extremity. Likewise, clonic afterdischarge in the contralateral upper extremity, produced by stimulating the "arm" area of area 4γ with a stimulus of greater than threshold intensity, could be abolished by stimulating this suppressor area just anterior to the superior precentral sulcus This finding has since been confirmed in still another patient.

Paralysis—Removal of the representation of one or both of the extremities from the precentral motor cortex in man results in an immediate complete flaccid paralysis of the part or parts represented. It is true that in Case 1 the hip and knee were not completely paralyzed, but the extirpation of the "leg" area can not be regarded as complete in that instance. Also, the slight power of extension of the knee which was preserved in Case 4 must be regarded as a slight exception to the above statement. Furthermore, in the patient P de F mentioned above, only the "arm" and "leg" areas were removed from area 4γ. Although the arm was immediately completely paralyzed it began to recover in a few days—much more quickly than after removal of both areas 4 and 6. The lower extremity could be moved quite forcefully at the hip immediately after the operation and also showed a much earlier onset of recovery than is usual after the more extensive extirpations.

This paralysis after removal of both areas 4 and 6 is temporary, and recovery begins in from four to sixteen days after the operation. The order

of recovery is variable, and that part which first begins to recover is not necessarily the one which recovers most completely. In some instances the fingers were the first part of the upper extremity to show any recovery of voluntary movement. It is true that in Case 2, where the fingers were the first part to recover, all of the "finger" area may not have been removed.

Once recovery has begun, it always progresses most rapidly in those muscles moving the proximal joints. In the final picture the paresis is always much greater in the muscles moving the distal joints, and some muscles in those regions may remain permanently paralyzed.

The ultimate deficit is less in either the arm or the leg when the representation of that extremity alone is destroyed. It is considerably greater in both the arm and the leg when the representation of both is removed.

In the upper extremity, the recovery is greater in the flexor muscles. In fact, the extensor muscles of the wrist and fingers may never recover. Supination of the wrist was usually more defective than pronation.

In the lower extremity recovery is greater in the extensor muscles than in the flexors. Movement of the toes often remains feeble or absent, and dorsi-flexion of the foot is much weaker than plantar flexion.

Spasticity—The paralyzed extremity is flaccid on passive manipulation immediately after the operation. Within one to two weeks spasticity appears and slowly increases in intensity. It is doubtless significant, although the actual relationship is not clear, that both recovery of voluntary power and development of spasticity are most marked in the same general group of muscles, i.e., the flexors of the upper extremity and the extensors of the lower. These two phenomena do not go hand in hand, however, for, whereas the recovery of voluntary power is greatest proximally, the spasticity is greatest distally.

This spasticity is of a clasp-knife type and thus is characterized, like the spasticity of the experimental decerebrate state, by the lengthening and shortening reactions. The spasticity, though always present, is not severe. It is not of the intensity commonly seen with capsular hemiplegias, and when the patient is walking the upper extremity does not assume the typical flexed or semiflexed posture but hangs downward at the side. Like the spasticity seen with hemiplegia, Little's disease, multiple sclerosis, etc., the spasticity here is enhanced by emotional excitement and by cold.

It is true that in Case 3 the immediate post-operative state was not a flaccid one. As previously pointed out, however, I believe this to be due to the presence of pre-existing pathology. Fulton and McCouch (1937) have shown in subhuman primates that if the precentral region is removed sometime prior to transection of the spinal cord, the characteristic flaccidity and areflexia do not appear or are of unusually short duration. In

Case 3 it is my belief that the injury to the precentral region or its projection fibers some 16 months prior to the operation so conditioned the subcortical and spinal reflex centers that they assumed this state of hyperreflexia more promptly than they would otherwise have done.

Reflexes—The tendon reflexes, i.e., biceps, triceps, radial, knee, and ankle jerks, are usually present and even hyperactive immediately after the operation and remain so In Case 2 they were abolished for the first three post-operative days and were feeble until after the nineteenth post-operative day, since when they have been hyperactive. When the "arm" area has been destroyed, Hoffmann's sign, also a stretch reflex, usually appears somewhat later, and thereafter remains present. As the tendon reflexes increase, clonus can usually be elicited at the wrist, fingers, patella, and ankle.

Reflex forced grasping has not often been excitable in any of these cases, has never been marked, and even when present has always been very transitory.

Babinski's sign appears shortly after destruction of the uppermost part of the precentral gyrus, but within how many hours I am unable to state. It has been observed on the day of operation, in some cases, and on the first post-operative day, in others It frequently is present even when the uppermost part of the precentral gyrus has not been removed, but under these circumstances does not persist

Though the abdominal reflexes on the side opposite the removal of the precentral cortex are usually diminished and may even be abolished, this condition does not persist. They usually, subsequently, return to their pre-operative activity.

Atrophy—In all the cases where careful observations have been made, atrophy has occurred in those muscles whose precentral cortical representation has been removed, even though these muscles are not completely paralyzed and are not flaccid. It is true that this atrophy is by no means comparable to that which occurs when the anterior horn cell or the peripheral nerve is destroyed. Yet, it is gross enough to be obvious on inspection and is confirmed by actual measurement. In those cases where some atrophy was present prior to the operation it has progressed.

Sensation—In every case reported here, there have been marked alterations in sensation which were present on the first post-operative day and persisted for a variable period of time thereafter. In patients who have been subsequently operated upon great care has been taken to examine sensibility as soon as possible following the operation. We have now convinced ourselves that there is no sensory loss immediately after extirpation of the precentral gyrus, but that the sensory loss appears several hours later when edema, hemorrhage and subsequent interference with cir-

culation have had time to affect the functional activity of the post-central region. (These cases will be reported in detail elsewhere.) There is considerable variation in the duration of the sensory loss and in the modalities of sensation involved. Thus, in Case 2 all forms of sensation, light touch, pin-prick, position-sense perception of vibration, stereognostic sense, the recognition of objects, two-point discrimination, the perception of figures written in the palm, and the identification of digits touched were all abolished. By the third day, the perception of light touch had begun to return, position-sense and vibratory sense began to return the following day, while recognition of objects placed in the hand, two-point discrimination, and identification of figures written in the palm of the hand were slowest in recovering. Ultimately all sensory defects completely disappeared. In contrast is Case 4, with a more extensive extirpation. In this instance the loss was far less. The perception of light touch, pin-prick, and vibration were never affected. Position sense was temporarily abolished from the fingers but not from the toes. Similarly the ability to identify the finger which was touched was temporarily lost while the ability to recognize the toes was only diminished for a short time. The ability to recognize objects placed in the hand and figures written in the palm was reduced but never abolished.

Recovery of these diminished or abolished sensory abilities usually began in from four to ten days, and recovery was complete in from fifteen days to several months

Vasomotor Control—Careful studies of the changes in the temperature of the skin were made only in Case 3. These limited observations indicate that removal of the precentral motor cortex is associated with a very temporary vasoconstriction in the skin of the part whose cerebral representation has been removed

CONCLUSIONS

Innervation of Purposeful Movement

It is a well-established fact that in the carnivora, e.g., dog and cat, the motor cortex, i.e., the sigmoid gyrus, or for that matter, all of the cerebral cortex is of relatively little importance in the control of the activity of the skeletal musculature. Dogs and cats from which the entire cerebral cortex has been removed still stand and walk almost as well as normal animals (Schaltenbrand and Cobb, 1930). However, in the primates this is not true. The process of encephalization has progressed to the point where the precentral cortex has assumed most of the control over the skeletal musculature, and when the precentral motor cortex is removed from both

cerebral hemispheres these animals become almost totally paralyzed and remain so even after forty-eight days. They are unable to sit, stand, walk, climb, grasp food and carry it to their mouths, etc. In fact, all movement is abolished except for reflex activity and certain stereotyped grasping and pulling movements[1] (Bucy and Fulton, 1933; Bieber and Fulton, 1938).

Although similar observations have not been made in man, there is no reason to believe that encephalization is less complete in human beings than it is in subhuman primates. It is true that Foerster (1936) has produced movement of skeletal musculature by electrical stimulation of many other parts of the cortex (an observation which Penfield and Erickson, 1941, and Penfield and Boldrey, 1937, were unable to confirm, except for the post-central gyrus) and that Levin and Bradford (1938) demonstrated that in the macaque a few of the fibers of the pyramidal tract arise in the parietal cortex. However, if these areas outside the precentral motor cortex contribute at all to voluntary muscular activity, their contribution is such that it is ineffective in the absence of the precentral areas. It is thus obvious that in primates practically all voluntary movement results from the activity of the precentral motor cortex. When, after removal of one part of this cortex, some movement recovers, this must, therefore, result from the activity of some remaining part of the precentral motor cortex but not from the activity of some other cortical area outside the precentral region or from the activity of the basal ganglia as has so often been assumed.[2]

In experimental animals (macaques, baboons, etc.) this is readily demonstrable (Bucy and Fulton, 1933; Bieber and Fulton, 1938; Wyss, 1938). Area 6 or area 4 in one hemisphere alone is capable of producing very useful purposeful movements in all four extremities. And yet, when that one last remaining area is removed, the animal becomes helpless. This leaves no doubt that both area 4 and area 6 have extensive control over the ipsilateral, as well as the contralateral extremities, far in excess of what one would anticipate from the very limited movements which can be produced

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[1] Through personal communication Dr Marion Hines informs me that in her experience bilateral removal of areas 4 and 6 has not produced quite as severe a motor deficit as we observed at New Haven. Woolsey and Bard (1943) have also recently reported, in abstract, that when areas 4 and 6 were removed from both cerebral hemispheres of a monkey in stages with intervals of many months to two years between the various operations the deficit was by no means as great as when the same operations were performed at much shorter intervals. After these extirpations their animal, although greatly incapacitated, was able to walk, and, when excited, to climb. It will be most interesting to see if the same results can be obtained in more than one animal.

[2] There is one likely exception to this statement Kennard (1936) has pointed out that removal of the precentral motor cortex bilaterally from infant monkeys does not abolish voluntary movements as it does in the adults. It is thus possible that in human beings, too, the basal ganglia or some other part of the cortex may be capable of integrating voluntary movements when the precentral cortex is destroyed before, at, or shortly after birth.

in the ipsilateral extremities by electrical stimulation of the cortex (Bucy and Fulton, 1933). In fact, in monkeys, movement in the ipsilateral upper extremity was always very difficult to obtain by electrical stimulation and frequently could not be obtained, yet in every case ablation experiments demonstrated extensive ipsilateral innervation in the upper extremity. It has been very difficult to produce movement in the ipsilateral extremities by stimulation of the cerebral cortex in man (Penfield and Erickson, 1941). Recently, however, Rasmussen and Penfield (1947) have succeeded in producing movement at both hips from the stimulation of a single cortical point.

Considerable evidence exists as to the effect of the complete removal of the precentral motor cortex in man. Dandy (1928, 1933), Gardner (1933), Rowe (1937), and others have removed most of the cerebral cortex of the right hemisphere, including all of the precentral motor cortex. In such cases if, as has just been pointed out, all voluntary movement is dependent upon the precentral motor cortex, we may assume that all of the movement which persisted in or returned to the extremities contralateral to this extirpation was the result of activity in the ipsilateral precentral motor cortex.

The greatest recovery was shown in Gardner's (1933) case (O'Brien, 1936). His patient was a 31-year-old woman. At operation on August 31, 1931, he removed practically the entire cortex of the right cerebral hemisphere; only most of the basal ganglia and a portion of the uncinate gyrus were left. The claustrum was removed along with the cortex. Immediately after the operation a complete left hemiplegia was present. About five weeks after the operation, when supported between two nurses, she was able to move the left lower extremity in walking but unable to move this extremity when seated or when lying in bed. A few weeks later she was able to flex and extend that extremity when in bed, and voluntary power gradually increased thereafter. On examination, twenty months after the operation, the left palpebral fissure was wider than the right, the left masseter and temporal muscles contracted somewhat less forcefully than those on the right, but the jaw did not deviate on opening. There was a questionable or very slight weakness of the left orbicularis oculi and of the left side of the face about the mouth. She was able to walk well without support and to go up and down stairs unaided. There was considerable power of flexion and extension of the knee and hip but no voluntary movement of the ankle or toes. The left upper extremity was useless and there was no voluntary power. The left extremities were spastic, the tendon reflexes were increased, and Babinski's sign was present. On the left side the abdominal reflexes were abolished. There were marked sensory changes and a complete left homonymous hemianopsia.

In 1933 Dandy reported the analysis of three similar cases which had been operated upon earlier. Two of these are of interest to our study In Case 1 he removed the right cerebral hemisphere except for a part of the occipital lobe, the medial and postero-inferior part of the temporal lobe and the basal ganglia on June 4, 1923 Approximately seven weeks later the left arm was completely paralyzed, the left leg could be flexed at the knee but not extended There was no increased resistance to passive manipulation, but the tendon reflexes were greatly increased. The abdominal reflexes were all present and equal, whereas earlier they had been abolished on the left side. Although the patient survived for two more years, no further observations are reported.

In Case 2 the right cerebral hemisphere, except for the basal ganglia, was removed. The patient developed no movement in the upper extremity and only slight movement of the foot, but no movement of the toes, hip, or knee.

In none of Dandy's cases was the movement in the lower extremity sufficient to allow the patient to walk.

In Rowe's (1937) case, six months after the operation, the patient was able to raise the left arm only about six inches from her lap, but power in the left leg recovered to "about 75 percent of normal on individual movements" and she was able to walk with the aid of a brace.

It is obvious from these studies that even after removal of the entire precentral motor cortex on one side, it is possible for the patient to recover sufficient voluntary control over the lower extremity to permit him to move the extremity at the hip and knee and to walk quite well. As has been previously pointed out, all the evidence points toward such recovery being due to innervation from the ipsilateral precentral motor cortex. On the other hand, all the evidence indicates that in the adult man there is not sufficient ipsilateral innervation to produce any movement of the upper extremity. There is no evidence that the basal ganglia can produce voluntary movement in either extremity in the adult human being.

Accordingly, in the cases recorded here, it must be concluded that all movements in the upper extremity must be due to the function of that part of the contralateral precentral motor cortex which was not removed. As might be anticipated, the amount of movement appears to be roughly proportionate to the amount of precentral motor cortex left. Thus, when only the "arm" area is removed and the "leg" area as well as the lower part of the precentral motor cortex is left behind, as in Case 2, the amount of movement which recovers is much greater, particularly in the distal parts of the extremity than in those instances, e.g., Case 4, where both the "arm" and "leg" areas are removed. Even in that case, however, the

lower part of the precentral area alone is able to establish a very full range of strong movements at the proximal joints.

In the case of the lower extremity, it is not possible from these studies to ascertain how much of the recovery was the result of ipsilateral and how much the result of non-somatotopic contralateral innervation. However, the fact that in all of my cases, including several not recorded here, where there was considerable preoperative hemiparesis useful movement sufficient to allow them to walk well returned, would seem to indicate, in comparison with Dandy's experience, that the contralateral innervation played no small part. The practically complete recovery of movement of the foot and toes in Case 1, in contrast with all other cases where more of the leg area was extirpated, would indicate that area 6 in this region is quite capable of establishing practically normal movement independent of area 4γ which was largely removed.

It is obvious in all cases where the representation of both the arm and leg is removed that the recovery is greater in the leg than in the arm. However, it should be pointed out that this difference is often not as marked as it appears. The reason lies in the functional activity of these two members. The lower extremity is primarily a support and a rigid leg which can be moved from the hip and to a lesser extent at the knee is a very useful member of the body. But an upper extremity, being primarily prehensile, which can be moved to the same degree at its two proximal joints but whose distal joints are rendered immobile, is almost useless.

It should also be pointed out that whereas the principal cortical representation of an extremity in the "arm" or "leg" area of the precentral gyrus is concerned with all movements, the secondary areas which take over activity when the primary ones have been destroyed are capable of establishing movement only in the proximal joints. This is true whether the secondary areas be other parts of the contralateral precentral motor cortex or, in the case of the leg, are in the ipsilateral cortex.

Atrophy

It has been commonly taught that whereas atrophy characterizes destruction of the "lower motor neuron" it is not present with lesions of the "upper motor neuron." Like most generalizations this is only relatively true—Head and Holmes (1911) and more recently Winkelman and Silverstein (1932) have commented on the occurrence of atrophy with "post-central lesions." Fulton (1938) is of the opinion that in these cases the atrophy results from encroachment of the lesion upon area 4. Fulton (1938) himself observed in the chimpanzee an atrophy of from 30 to 50 percent in the affected muscles after destruction of area 4, but such atro-

phy was notably absent following removal of the postcentral convolution and other parts of the parietal lobe.

The present cases clearly demonstrate that measurable atrophy will also develop in man following destruction of areas 4 and 6 together It is certain that such atrophy is not as severe as that which follows sectioning of the peripheral motor nerve or destruction of the anterior horn cell, and it is likely that the atrophy following removal of area 4γ alone is greater than that following ablation of the entire precentral motor cortex (areas 4 and 6).

I agree with Fulton (1938) that this atrophy is probably the result of disuse. The greatest disuse is with a flaccid paralysis, hence the greatest atrophy. With spastic paralysis the muscles are engaged in reflex muscular contraction, even though not in voluntary activity, hence atrophy is not as great with spastic as with flaccid paralysis. As a relatively more flaccid paralysis results from destruction of area 4γ alone, whereas a spastic paralysis follows destruction of areas 4γ, 4a, 4s, and 6, atrophy is probably greatest with lesions of area 4γ alone.

Spasticity and Hyperreflexia

Fulton and his co-workers have thoroughly established the fact that, in subhuman primates, the precentral motor cortex controls the postural reflexes by inhibition. It is obvious from the cases recorded here that the same is equally true for man. By their nature, these cases throw little light on the presence or activity of the "strip" area (area 4s) lying between areas 4a and 6, which Hines (1936, 1937) has shown to be that part of the precentral motor cortex in subhuman primates which is most concerned with this inhibition It is not unreasonable to assume that such a strip exists in man, and as noted above (p. 380) I have recently been able to demonstrate its presence physiologically in two cases (Bucy and Carol, 1944). Bonin (Chapter II) calls attention to the fact that in man there is a narrow band of cortex with its own peculiar cytoarchitecture lying along the precentral sulcus between area 4a and area 6 (frontispiece).

While the nature and distribution of the spasticity is the same as that seen in the usual capsular hemiplegia, it is not as severe. It involves principally, though not exclusively, the flexor muscles in the upper extremity and the extensor muscles in the lower extremity. Like the spasticity associated with capsular lesions and that seen in the decerebrate cat, it is a "clasp-knife" spasticity, characterized by the lengthening and shortening reactions, and associated with hyperactivity of the tendon reflexes. However, to repeat, in none of my cases did the spasticity after the operation

become as severe as that commonly seen after capsular lesions. This is well illustrated by the fact that in all cases the arm hung at the side when the patient was walking and did not assume the flexed or semiflexed position, so commonly seen in capsular hemiplegias.

Similarly Dandy (1933) in his Case 1 noted that almost seven weeks after removal of most of the right cerebral cortex, including all of the pre-central motor cortex, there was no increased resistance to passive manipulation, although the tendon reflexes were greatly exaggerated Gardner (1933) in observing his patient twenty months after a similar operation gives little detail but noted "spasticity which varied from time to time" Rowe (1937) states that six months following such an operation he found the upper extremity to be "moderately spastic" and that it "shows no contractures." He does not comment on the spasticity in the lower extremity.

Furthermore, it is a common experience that the spasticity associated with lesions in and about the mid-brain (Bailey, Buchanan, and Bucy, 1939) or with destructive lesions in the spinal cord is far greater than that seen with cortical or capsular lesions But in such instances the nature of the spasticity is not altered; it is merely increased in intensity

These facts in no way argue against the inhibitory action of the pre-central motor cortex on the postural reflexes which when released give rise to spasticity. They merely indicate that the cortical inhibitory control is re-enforced by various subcortical centers before it impinges upon the final common pathway in the spinal cord Present evidence (McCulloch Graf, and Magoun, 1946; and others; see also p. 265) indicates that the inhibitory influence passes downward from area 4s (and probably the other suppressor strips, areas 8, 2, 19, and 24) to the bulbar reticular formation and thence via the ventro-lateral fasciculus of the spinal cord to internuncial neurons in the anterior grey horns and then on to the anterior horn cells It seems likely that this complex mechanism is not merely a simple relay for the transmission of inhibition from the cortex to the final common pathway. The observed facts indicate that the mechanism itself contributes something to this effect

Forced Grasping

Forced grasping, as Bieber and Fulton (1933, 1938) pointed out, is part of the righting-reflex mechanism In the subhuman primate, it is under the control of area 6 and appears when that area is destroyed. In man forced grasping is usually associated with destructive lesions in the posterior part of the first frontal convolution (Adie and Critchley, 1927; see also Chapter XVI). Our experiences reported here, in which forced grasp-

ing was not seen, indicate that the region concerned with the inhibition of this reflex does not occupy the most posterior part of the first or second frontal convolution. It may be somewhat farther forward.

Babinski's Sign

The observations recorded here are in complete accord with the conclusion reached by Fulton and Keller (1932a) that Babinski's sign becomes obtainable after the uppermost part ("leg" area) of area 4γ (the area gigantopyramidalis) or its projection fibers are destroyed.

Abdominal Reflexes

These observations raise some most interesting questions about the abdominal reflexes. Removal of the precentral motor cortex may temporarily reduce or even abolish the contralateral abdominal reflexes but subsequently they return and usually regain their original intensity. Dandy (1933; Case 1) noted a similar effect after removal of the cortex of the right cerebral hemisphere, whereas Gardner (1933) found the abdominal reflexes absent twenty months after such an operation. Similarly, it is a common experience to find the abdominal reflexes active in an individual with a congenital cerebral spastic paraplegia (Little's disease).

These facts certainly indicate that the statements frequently made that the reflex are of the abdominal reflexes passes up the spinal cord to the precentral cortex and thence back down via the pyramidal tract to the anterior horn cell, or that the precentral motor cortex or the pyramidal tract are primarily concerned with this reflex, are in error.

Vasomotor Control

Unfortunately accurate observations were not made in a sufficient number of these cases to justify any definite conclusions, but the findings in Case 3 support the experimental observations of Kennard (1935a, 1936a, 1937, and Chapter XI). There can be little doubt that the precentral motor cortex is concerned in some measure with the control of the vasomotor mechanism, as I have previously pointed out (Bucy and Case, 1939; Bucy, 1935a).

Sensation

Horsley (1909) was definitely of the opinion that the precentral gyrus was concerned with sensory perception Dusser de Barenne (1935), as the result of animal experimentation, was similarly impressed. The observations in the cases reported here might readily be similarly interpreted

Certainly profound sensory disturbances occurred. Their relatively short duration does not mitigate against Horsley's view, but might only indicate that the sensory functions served by the precentral gyrus were, after its destruction, taken over by other parts of the central nervous system.

However, certain facts have led me to doubt that the observations made here indicate that the precentral gyrus has anything to do with conscious sensory perception. One can not help being struck by the fact that the sensory deficit developing after extirpations of the precentral motor cortex varies tremendously. The various modalities of sensation were not always similarly affected in the different cases. In some the perception of light touch and of the pain produced by the pricking of a pin were profoundly affected, even lost, whereas in other instances these particular sensations were affected but slightly. This would certainly seem to indicate that whatever is responsible for the sensory change is far more variable and less definite than the removal of the precentral gyrus which was common to all of the cases. Recently, however, careful observations have been made in two cases which seem conclusive in this connection. They will be briefly recited.

CASE 5

E S, a young man 27 years old was admitted to the Illinois Neuropsychiatric Institute on February 11, 1942. Since a few months after an acute febrile illness presumably an encephalitis at the age of five years, he had suffered from a left spastic hemiparesis and a left unilateral athetosis.

There was no sensory disturbance found on examination. On the afternoon of February 24, 1942, the right central area was exposed and the area stimulated. After delimitation of the "arm" and "leg" areas in the precentral gyrus they were extirpated. Posteriorly the extirpation was car-

Shoulder
Arm and
wrist
Hand
Fist of fingers
Little finger
L lower lip
L mouth
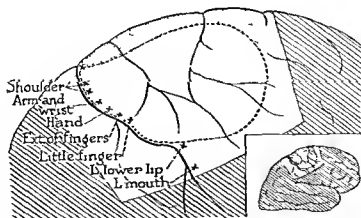
Fig 119 (Case 5) —Diagrammatic sketch of the field exposed at operation. The crosses just anterior to the central fissure indicate the points from which electrical stimulation evoked movement in the parts on the left side of the body listed on the left. The area extirpated is circumscribed by a broken line. The stippled area is the portion of the cortex which was destroyed by extensive undercutting

ried out subpially in order to avoid injuring the rolandic vessels and the postcentral gyrus as much as possible Anteriorly, the extirpation included part of the first and second frontal convolutions (fig 119). He returned to his room at 6 15 p m, following the operation. He was responding well at 8 15 p m. At 10 00 p m, examination by Dr Irving J Spiegel revealed a complete left hemiplegia with slight increase in resistance to passive movement. The tendon reflexes were increased on the left side as before the operation The abdominal and cremasteric reflexes were present bilaterally and equally. Perception of light touch was diminished on the left side and stimulation with cotton produced a burning sensation Perception of pin-prick, vibration, and position of the digits were only slightly diminished on the left side Stereognostic sense was very poor The following day, awareness of light touch and pin-prick were only slightly diminished, but position sense and vibratory sense, as well as stereognosis, were profoundly affected On the second post-operative day, the perception of light touch was markedly diminished, while pain sensibility remained only slightly affected Within a few days, sensation began to recover When he was discharged on March 24, 1942, one month after the operation, it was practically normal except for a slight defect in stereognosis. The involuntary movements were abolished and movements of the left arm and leg were as good as before the operation The involuntary movements were still abolished fourteen months after the operation (April 28, 1943) The hemiplegia was approximately as before the operation, but he walked better because there was no longer any interference from the involuntary movements. He is employed full time in an industrial job.

CASE 6

H Z, a young man 22 years old, was admitted to the Illinois Neuropsychiatric Institute on May 18, 1942 He had suffered from a left spastic hemiparesis and left unilateral athetosis since the age of six months The cause was unknown Pneumoencephalographic studies revealed a large calcified mass in the region of the right basal ganglia There were no sensory deficiencies. On the afternoon of June 16, 1942, the "arm" area of the right precentral region was removed and the "leg" area extensively undercut (fig 120) He returned to his room at 6 00 p m At 11 00 p m he was responding well At 11 30 p m he was examined for perception of pin-prick and no defect was found The following morning the same was true but by noon a slight hypalgesia was present in the left lower extremity There was no loss to light touch
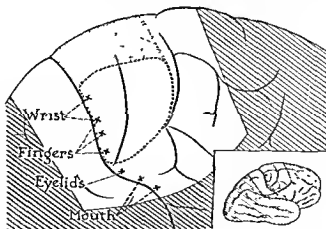
Fig 120 (Case 6)—Sketch of the field exposed at operation The results of electrical stimulation are indicated on the left The area extirpated is circumscribed by a broken line, the region which was undercut is stippled

or vibration and the sense of position was intact Stereognosis was definitely deficient in the left hand The left arm was completely paralyzed but some voluntary movement was possible in the left lower extremity That evening the sensory status was unchanged and he was able to recognize correctly numbers written in the left palm On the second post-operative day the slight hypalgesia persisted two-point discrimination was diminished, numbers written in

the left palm were no longer recognized, and sense of position was grossly defective Wheo he was discharged from the hospital two weeks after the operation there was some improvement in sensation The involuntary movements are abolished and he has since recovered as good a use of his left extremities as he had before the operation The involuntary movements were still completely abolished 10 months after the operation (April 28, 1943)

In these two cases there was little evidence of sensory loss soon after operation. In still others (which will be reported in detail elsewhere) special attention was paid to this point. They were examined as early as possible following operation and no evidence of any sensory loss was demonstrable. But within twenty-four hours the sensory loss was obvious, soon became profound and remained so. as in the other cases, for many days. These cases strongly indicate that the sensory loss which develops following these operations is not the result of removal of the precentral motor cortex but appears later. after edema and vascular alterations have had an opportunity to interfere with the activity of the cortex lying posterior to the central fissure.

Bowel and Bladder

The cases recorded above throw no light on the question of the representation in the precentral motor cortex of the voluntary control over the rectum and bladder and their sphincters It is generally believed that the cortical control over these structures is located bilaterally in the paracentral lobules. Certainly neither in the cases recorded here nor in any other case in which I have operated has a unilateral lesion of the precentral motor cortex, including the paracentral lobule, resulted in any disturbance of the functions of either bowel or bladder. Numerous observers have, however, reported such disturbances following bilateral lesions in this region. The following is a typical example. Unfortunately, however. it does not assist us in the precise localization of these functions.

CASE 7

F M. female. 31 years of age, was first admitted to the University of Chicago Clinics on January 7, 1938 In June of 1937 she had begun to suffer from localized convulsive seizures involving the left leg Weakness and atrophy of that extremity and numbness of the third and fourth fingers of the left hand gradually developed as these attacks recurred Examination revealed a left

spastic hemiparesis which was more intense in the lower extremity and a slight diminution of vibratory and position senses on the left side On January 11, 1938, an angioblastic meningioma was removed from the right upper central region A small nodule was left in the superior longitudinal sinus Following the operation the bowels and bladder functioned well A severe weak-

ness of the left arm persisted She was discharged from the hospital on January 21, 1938.

She was readmitted on December 6, 1940 She had had no convulsions and had been able to be up and about doing her own housework In November, 1940, she had developed weakness in the right leg and for two weeks before this admission the right arm had been growing weaker On December 7, 1940, a meningioma completely occluding the superior longitudinal sinus and extending to either side but mostly to the left, was completely removed Immediately following the operation she had a complete paraplegia with retention of urine Monro tidal drainage was instituted At first the bladder was atonic but by the fifth postoperative day (12-12-41) it had become hypertonic Gradually the tone diminished, and the tidal drainage was discontinued on the eleventh post-operative day Following

the operation she had marked discomfort from intestinal distention, requiring the frequent use of rectal tubes and enemas The first spontaneous bowel movement occurred on the seventh post-operative day The right arm was strong immediately after the operation The legs recovered slowly On January 28, 1941, fifty-two days after the operation, her physician, Dr H R Varney of Kewanee, Illinois, reported that the bowel movements were regular and normal There was no disturbance of the functions of the bladder except that laughing would at times cause slight involuntary dribbling of urine When last seen on July 20, 1942, over eighteen months after the last operation, she had perfect control over both the bowel and bladder and they functioned normally. However, a marked spastic weakness of both lower extremities still persisted

Langworthy, Kolb, and Lewis (1940) have pointed out that the cerebral cortex exercises a control over the reflex activity of the bladder similar to its inhibitory control over the postural reflexes of the skeletal musculature. When this cortical control is removed a hyperreflexia develops, characterized by urgency, frequency, limited capacity, and a markedly heightened contractility of the bladder in response to rapid filling.

Chapter XV

RELATION TO ABNORMAL INVOLUNTARY MOVEMENTS

Paul C. Bucy, M.S., M.D.

Professor of Neurology and Neurological Surgery
University of Illinois College of Medicine
and
Attending Neurologist and Neurological Surgeon
Illinois Research and Educational Hospitals
and The Chicago Memorial Hospital
Chicago

OUTLINE OF CHAPTER XV

Involuntary Movements

INVOLUNTARY MOVEMENTS

WITHIN RECENT YEARS clear-cut evidence has been produced establishing the relationship of the precentral motor cortex to various abnormal involuntary movements of the skeletal musculature. This demonstration had been anticipated many years before by a few physicians endowed with a very keen insight, but their observations and deductions had been largely either forgotten or ignored prior to the last decade. Parkinson as early as 1817 had observed that the tremor at rest characteristic of the "shaking palsy" disappeared following the development of a hemiplegia from an apoplectic ictus. Horsley in 1909 reported that in three cases of unilateral athetosis he had abolished the involuntary movements by removing the precentral gyrus. Others had made similar observations both as to the tremor of paralysis agitans (Patrick and Levy, 1922) and as to athetosis (Anschütz, 1910; Payr, 1921; Nazaroff, 1927; Polenow, 1929) However, it remained for Kinnier Wilson (1929) by a very careful consideration of the entire problem to reach the conclusion "Since the movements [of choreo-athetosis] are active and continuing, for their existence relative integrity of some efferent path is a *sine qua non*. Many cogent arguments suggest that this path is the corticospinal path." However, although Kinnier Wilson was of the opinion that the corticospinal path conducted the impulses responsible for the involuntary movements to the spinal cord, he did not believe that the Betz cells or the area gigantopyramidalis could produce such movements unaided. He reasoned: "For the complex movements of chorea, to take an example, we must postulate a motor centre higher in a physiological sense than that of the rolandic motor region, and both clinical, pathological, and experimental evidence suggests that such a centre lies in front of the rolandic area." How beautifully in this statement he saw the necessity for the existence of the premotor area lying in front of the area of the Betz cells—an area which was shortly to be demonstrated! In spite of Kinnier Wilson's well-reasoned conclusions, the neurological world was hesitant to accept them and awaited more positive direct proof.

Choreo-Athetosis

In 1932, Buchanan and I reported a confirmation of Horsley's observation that removal of the precentral region would abolish the involuntary movements of athetosis. Since then I have repeatedly made the same observation (see Cases 5 and 6 in Chapter XIV). As many of these cases have recently been reported in detail (Bucy, 1940), they will not be re-

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corded here. In 1935, Sachs reported a similar confirmatory series of three cases. By other neurosurgeons I have been informed of several similar observations which have not been published.

Although Bucy and Buchanan (1932) postulated that "the athetoid movements were effected by the area 6aα, . . . , and that this area produced its effect by efferent impulses which passed via subcortical (extrapyramidal) centres to the spinal cord and the anterior horn cells," it would be impossible to prove this contention without further evidence. The removing of the precentral region destroys both the pyramidal tracts and the parapyramidal tracts which arise from areas 4 and 6 and descend to subcortical centers (Bucy, 1936). Either might therefore be responsible for the involuntary movements of choreo-athetosis An earlier case of Jakob's (1932, Case 18) strongly indicated that the pyramidal tract was not concerned In that instance a patient with a luetic infection had a severe athetosis and subsequently developed a hemiplegia. With the onset of the hemiplegia the athetosis vanished, and though the hemiplegia lasted but a few days and then almost completely disappeared the athetosis never recurred during the remaining eighteen months of the patient's life. As it must be assumed that the pyramidal tract received only minimal injury in this case, it seems likely that the involuntary movements were produced by some other fiber system which was more completely destroyed. Further indirect evidence in support of this view was presented by Bucy and Case (1937; see also Bucy, 1940). They demonstrated that large doses of the barbiturates will abolish the involuntary movements of choreo-athetosis for many hours after the patients have awakened from the sleep induced by the drug and have regained voluntary control over their extremities almost comparable to their control before the drug was given. Fulton and Keller (1932) had shown that although the barbiturates depress in some measure the excitability of area 6 they almost completely suppress that of area 6. It was for this reason that in studying the electrical excitability of area 6, I had chosen ether as the anaesthetic agent (Bucy, 1933). In view of this selective *depressant action of the barbiturates for area 6 it was* concluded that the selective action of these drugs on the involuntary movements of choreo-athetosis was further evidence that the pathway responsible for these movements was the parapyramidal rather than the pyramidal system.

As it is impossible to destroy separately either the pyramidal or the parapyramidal system by a cortical lesion or by a lesion in the internal capsule, there being considerable overlap of the two systems in both places, it remained for Putnam (1933 and 1938) to perform the crucial experiment. He demonstrated that the involuntary movements of choreo-athe-

tosis can be materially diminished or even abolished by destruction of the anterior fasciculus of the spinal cord without injury to the lateral cortico-spinal tract. This leaves little doubt that the cortical extirpations are effective because they destroy the efferent fibers originating from the pre-central motor cortex other than the pyramidal tract, i.e., the parapyramidal system.

The fact that these anterior cordotomies do not always completely abolish the involuntary movements or do not abolish them permanently does not appear to me to be argument to the contrary. For instance in a case previously reported (Bucy, 1940, Case 5), an anterior chordotomy by Oldberg abolished the athetotic movements completely for at least three weeks. They then returned to a slight extent but remained greatly dimin-ished for over a year and a half and never returned to their original severity. It seems obvious that this profound effect for over one and one-half years must be attributed to section of extrapyramidal fibers in the anterior fasciculus, and that the return of some involuntary movement must be attributed to some extrapyramidal fibers having escaped destruc-tion. At no time was there any reason to believe that the pyramidal tract had been injured by this operative procedure.

As Levin (1936) has shown, the parapyramidal system is a complex one (see Chapter V). It arises from the entire precentral motor cortex and descends to various subcortical nuclei, including the substantia nigra, the tegmentum of the mesencephalon, the pons, and doubtless the basal ganglia and numerous other loci. Which group or groups of these fibers are responsible for the movements of choreo-athetosis is not clear. As destruc-tion of the caudate nucleus and putamen is commonly associated with such disorders, it seems most unlikely that corticostriatal fibers could produce these movements. Until further evidence is forthcoming, this aspect of the problem must remain unsolved.

For the present we may conclude that the involuntary movements of choreo-athetosis are produced by nervous impulses arising from the pre-central motor cortex, traveling from there to some subcortical center, and thence being relayed by secondary or tertiary neurons down the spinal cord, via the anterior fasciculus to the anterior horn cells.

Tremor

Tremor, as a clinical manifestation, is divisible into two main groups which have no etiological connotations. They are tremor at rest and inten-tion tremor (also known as action tremor). Every tremor consists of an involuntary (unwilled) oscillating movement of a part, produced either by alternating contraction and relaxation of the muscles involved or by

alternating contractions of protagonists and antagonists (Hoefer and Putnam, 1940; Hoefer, 1940, fig. 223). Tremor at rest occurs in parts which are supported and which are not at the time involved by voluntary muscular contractions. Intention tremor occurs in the part when its musculature is being contracted voluntarily. Most such tremor is seen when the part is being voluntarily moved, but static tremor is another less common manifestation of intention tremor. Static tremor is present when the part is being voluntarily held still against the force of gravity, as when the head is held upright or the arm is held outstretched.

It is not to be assumed however that these two forms of tremor invariably occur separately. They are commonly present in the same individual. Although tremor at rest is typical of Parkinson's disease, intention tremor may also occur in this condition. Patrick and Levy (1922) found it in thirteen per cent of their 140 cases. In hepato-lenticular degeneration, Wilson's disease, both forms of tremor are usually present, although the action tremor is commonly the more violent. The first patient whose precentral motor cortex was removed for the relief of tremor suffered from both varieties as the result of a severe craniocerebral injury (Bucy and Case, 1939).

That tremor at rest might be mediated by the pyramidal tract was indicated early by Parkinson (1817) who found in his Case 6 that the tremor at rest which had been generalized was abolished from the right side during the two weeks that that side was paralyzed as the result of an apoplectic seizure. A similar observation was made by Patrick and Levy (1922). However the lesions in such instances of vascular disease are usually so diffuse or so extensive that discrete localization to one pathway is impossible. This has been clearly brought out by the recent careful pathological study of such a case by Balser (1942). Until the surgical attack upon this type of tremor, which was first made in October, 1937, there was no other evidence as to what neural mechanism produced and conveyed the impulses which produced the tremor. Obviously the subcortical centers which were previously destroyed by disease did not do so.

In view of the fact that intention tremor develops only when the affected muscles are voluntarily innervated, it is not surprising to learn that the precentral motor cortex and its efferent fiber systems are intimately connected with the production of such tremor. Aring and Fulton (1936) found that in monkeys the intention tremor resulting from decerebellation is abolished by the removal of the precentral motor cortex, areas 4 and 6.

With these facts as a background, I operated upon G. W. S. on October 12, 1937 (see Case 3 in Chapter XIV; also Bucy and Case, 1939; Bucy, 1940, Case 4). He was suffering from tremor both at rest and in association

with voluntary movements, following a severe craniocerebral injury. The tremor was confined to the right side, was violent in the upper extremity and relatively mild in the lower. The representation of the upper extremity in the left precentral region was determined by electrical stimulation and extirpated (fig. 117, p. 367). The tremor was completely abolished and has never returned. In another case, on January 11, 1940, the representation of the upper and lower extremities was removed from the right precentral region (fig. 118, p. 374) of a young man (C.M.L.) suffering from a typical parkinsonian state involving the left extremities (Bucy, 1940, Case 7; see also Case 4, Chapter XIV). The tremor occurred both at rest and with voluntary movement. Again the tremor was completely abolished and has remained so.

Subsequently Putnam (1940) reported two similar cases in which extirpation of the precentral gyrus resulted in a marked diminution of the tremor without quite abolishing it. It is noteworthy that his extirpations apparently spared the anterior wall of the rolandic fissure and were otherwise not as extensive as mine.

Obviously, it would be impossible to conclude from the observation of these human cases whether the pyramidal tract alone, the parapyramidal tracts, or all of the efferent fibers from the precentral motor cortex produced the tremor. These observations differ from those made by Parkinson, Patrick and Levy, and Balser in that they confine the effect to the precentral motor cortex, eliminating from consideration the other areas of the cerebral cortex and the subcortical structures.

However, again Putnam (1940) was to clarify the problem. Earlier (1938) he had demonstrated that section of the anterior fasciculus of the spinal cord did not affect the tremor of parkinsonism, and Foerster and Gagel (1932) had recorded a somewhat similar experience. It was therefore obvious that at least those parapyramidal fibers which mediate the nervous impulses responsible for choreo-athetosis were not concerned in the production of parkinsonian tremor. Having been informed by correspondence of our results following cortical ablation with G. W. S. on October 12, 1937, Putnam was stimulated to section the pyramidal or lateral corticospinal tract in the cervical spinal cord in such a case. This he did on March 4, 1938, with complete abolition of the tremor at rest but with the persistence of slight but perceptible tremor in association with voluntary movements. In all he has reported seven such operations (Putnam, 1940a, b) following which the tremor has been almost completely relieved in the affected arm and leg.

These observations of Putnam's leave little doubt that in man it is the pyramidal tract which is primarily concerned with the production of tremor. Recently Sachs (1942) has reported briefly an observation of his

which supports this conclusion. He removed tissue from the precentral region anterior to area 4 without affecting the tremor. It was only when the posterior part of the precentral gyrus was removed at a subsequent operation that the tremor was abolished. In a recent case (P de F, see p. 380; Bucy, 1945) tremor of long standing was immediately abolished by removal of area 4γ in the "leg" and "arm" regions. Later, however, a slight tremor returned to the involved extremities. I am, therefore, forced to conclude that to obtain a complete and permanent abolition of tremor the entire width of the precentral gyrus, from the central fissure to the precentral fissure, should be removed. This has been done successfully on several occasions.

It is impossible at the present time to correlate Klemme's (1940) observations with what has just been said about tremor. Unfortunately no detailed description of his operative procedure has appeared, and it is impossible to be sure just what portion of the frontal cortex is included in the term "premotor cortical excision" as used by him. As noted above Sachs (1942) reported that he failed to relieve tremor when the cortex anterior to the excitable motor cortex was extirpated and was successful only when area 4γ was removed. Putnam (1949a) states that White using the method outlined to him by Klemme "obtained only partial relief." Putnam himself was unable to stop tremor by infiltration of the "premotor" region with one per cent procaine hydrochloride or in another case by the removal of a "large area of cortex anterior to area 6." Klemme's series is by far the largest in which tremor has been treated by cortical excision The study of this extensive material will doubtless contribute greatly to our knowledge of the subject when it becomes available.

Meyers' (1940) observations are also difficult to evaluate. Of his eight cases four can hardly be included in this consideration. In Case 3 an extensive post-operative infection occurred; in Case 5 there was a hemiparesis post-operatively, making that case comparable to cases where an apoplectic hemiplegia or extirpation of the precentral motor cortex has abolished tremor; in Case 7 an early post-operative death occurred; and Case 8 had only been under observation a few days at the time of the report. In the remaining cases it appears that in three (Cases 1, 4, and 6) removal of the head of the caudate nucleus diminished but did not abolish contralateral tremor. In Case 2 removal of the heads of both caudate nuclei diminished the tremor on one side while it was increased on the other To these observations must be added Putnam's (1940a), who stated that in his case "the tremor was unaffected by removal of a large area of cortex anterior to area 6 and destruction of the head of the caudate nucleus." but that subsequently section of the anterior limb of the internal capsule resulted in a hemiparesis and abolition of the tremor.

Pathogenesis of Involuntary Movements

The relation of the precentral motor cortex to the actual transmission of impulses which produce choreo-athetosis and tremor seems clear. The relation of this area to the systems which are destroyed and thereby release the precentral efferent mechanisms to the production of involuntary movements is, however, speculative. As these hypothetical considerations have been recently fully dealt with elsewhere (Bucy, 1942). I shall present them only summarily here.

Fig. 121.—The neural mechanism of intention tremor. The inhibitory impulses arise from the precentral cortex (areas 4 and 6) pass through the corticopontine fibers to the pontine nuclei, thence up the opposite middle cerebellar peduncle to the cerebellar cortex, then to the dentate nucleus, upward through the superior cerebellar peduncle to and through the red nucleus (R.N.) to the postero-medial part of the ventro-lateral nucleus of the thalamus (V.L.), which in turn projects onto the precentral cortex, more onto area 4 than area 6. When this inhibitory mechanism is interrupted anywhere from the dentate nucleus to the ventro-lateral nucleus of the thalamus inclusive the removal of these inhibitory impulses from the precentral cortex results in the association of intention tremor with all of the voluntary movements produced primarily by the activity of the pyramidal fibers arising from area 4, and to a lesser extent, possibly, by the activity of the parapyramidal system.

Intention tremor commonly follows destruction of the cerebello-dentato-rubro-thalamic fiber bundle. As the neo-cerebellum, from which the impulses borne by this tract originate, receives much of its afferent innervation from the precentral motor cortex via the frontopontine fibers and possibly from collateral fibers from the corticospinal tracts, it appears

Fig 122—The neural mechanism of choreo-athetosis The suppressor or inhibitory impulses arise from the suppressor straps 8 and 4s and pass to the caudate nucleus (C N), they pass through the strio-pallidal fibers to the globus pallidus, thence from the internal division of the globus pallidus through the *fasciculus lenticularis* (*fl*) and *ansa lenticularis* (*a l*) into field H₂ and through field H₁ into the antero-lateral part of the ventro-lateral nucleus of the thalamus (V L); from there the thalamo-cortical fibers return the suppressor impulses to the precentral cortex, more to area 6 than to area 4 If this suppressor mechanism is interrupted in the *striatum* or the *globus pallidus* or the *thalamus*, the *parapyramidal* system arising from areas 4 and 6 will be released to abnormal activity, resulting in the involuntary movements of choreo-athetosis

This diagram also illustrates possible pathways for similar suppressor fibers from 8 and 4s to the caudate nucleus and globus pallidus and thence to the subthalamic nucleus of Luys (C Luys) either by way of the fasciculus and ansa lenticularis, and fields H₂ and H (Papez), or by way of a pallido-subthalamic bundle from the external division of the globus pallidus as described by Ranson and Ranson (1910) How these suppressor impulses return to the precentral cortex is unknown, but their interruption in the corpus Luys results in hemiballismus (This schema modified after Papez)

reasonable that we are dealing with a controlling circular neural mechanism from the precentral motor cortex to the cerebellum, and back through the thalamus to the precentral motor cortex (fig. 121). When this "governor" is destroyed the precentral motor cortex discharging via its efferent fibers functions abnormally, and voluntary movements become tremulous.

Choreo-athetosis is usually associated with destructive lesions of the caudate nucleus and putamen (Alexander, 1940), less commonly with destruction of the ventrolateral nucleus of the thalamus (Schuster, 1937), and still more rarely with lesions in the globus pallidus (Papez, Hertzman, and Rundles, 1938). It appears most likely that these various destructive lesions remove a "governor," thereby releasing the precentral motor cortex to an abnormal state of hyperactivity which finds expression via impulses travelling to the anterior horn cells through the parapyramidal fibers in the anterior fasciculus of the spinal cord. Anatomically these various subcortical nuclei are connected in a neural circuit which passes from the caudate nucleus and putamen to the globus pallidus and thence from the internal division of the globus pallidus through the ansa lenticularis and fasciculus lenticularis, through Forel's fields H_2 and H_1 into the ventrolateral nucleus of the thalamus, and from there by thalamocortical fibers to the precentral motor cortex (fig. 122) (cf. Bucy, 1942; Glees 1945) Dusser de Barenne, McCulloch, and their associates (1940a, b) have shown that this circuit when excited suppresses the electrical activity of the precentral areas 4 and 6, and further that this suppressor circuit is activated by two narrow bands of cortex lying in the precentral region (see Chapter VIII). One of these, known as 4s, lies between areas 4a and 6; the other 8, lies just anterior to area 6 (fig 91, pp 232-233). This is another circular neural mechanism. It passes from the precentral region via the caudate nucleus, globus pallidus, and thalamus back to the precentral motor cortex Its destruction releases the precentral motor cortex to hyperactivity similar to the effects of destruction of the precentral-cerebello-dentato-rubro-thalamo-precentral circuit discussed in connection with tremor

The anatomical connections by which the corpus subthalamicum of Luys exercises an influence on the precentral motor cortex, which when removed gives rise to hemiballismus, are as yet unknown. Likewise the anatomical, pathological, and physiological data are incomplete which are necessary to outline the suppressor mechanism whose destruction gives rise to tremor at rest The destructive lesions associated with Parkinson's disease are numerous and varied. Lesions of the substantia nigra are the most constant (Benda and Cobb, 1942), although the globus pallidus is also frequently involved (Alexander, 1940). With available anatomical knowledge it is possible to outline a circular suppressor pathway which may be

the one involved (fig. 123). It includes corticonigral fibers from the precentral region, thence from the substantia nigra to the globus pallidus (Ranson and Ranson, 1941) and then via the ventrolateral nucleus of the thalamus back to the precentral cortex. These neural connections exist. Whether they exercise a controlling influence over the precentral motor cortex has not as yet been demonstrated.

It should be noted that Benda and Cobb (1942), utilizing the same facts, arrived at quite another hypothesis. They likewise conclude that tremor at rest is produced by nervous impulses reaching the anterior horn cells via the pyramidal tract. But instead of visualizing a circular neural mechanism which controls the precentral motor cortex and the destruction of which gives rise to tremor at rest, they believe "the tremor is due to the
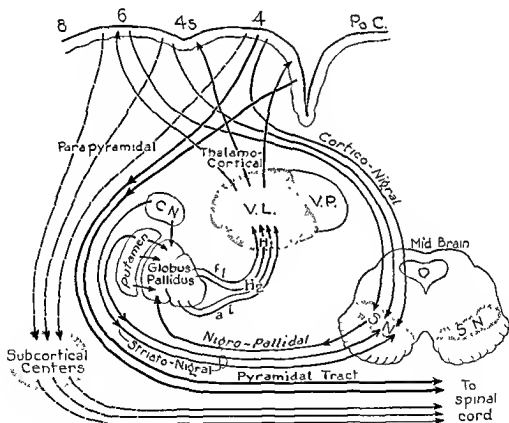
Fig 123—Probable neural mechanism of parkinson tremor The inhibitory impulses arise from the precentral cortex, pass through the cortico-nigral fibers to the *substantia nigra* (S N) thence to the globus pallidus, through the nigro-pallidal fibers recently demonstrated by Ranson, then to the ventro-lateral nucleus of the thalamus (V L), and back to the precentral cortex When this system is interrupted the abolition of its suppressor impulses allows tremor at rest (parkinson) to be produced primarily by impulses passing by way of the pyramidal tract.

fact that transmission of the motor nerve impulses is reduced and simplified to the primitive pattern of synchronized innervation, alternating in antagonistic muscle groups," because "the discharges conveyed through the extrapyramidal pathways (which distribute the phasic innervation and guarantee smoothness of action) are out of order." It is possible that this hypothesis finds some support in the recent observations of Hoefer and Pool (1943) that under certain circumstances, "The activity in the pyramidal tract occurs in bursts and groups of spikes synchronous with the cortical discharges, while the extrapyramidal activity is more continuous" I gather from the paper by Benda and Cobb that it is their opinion that the pyramidal tract "at rest," not involved in the execution of voluntary movements, delivers neural impulses to the anterior horn cells in rhythmical synchronized groups while the extrapyramidal fibers deliver nervous impulses at random This when both are intact the stimulation to the anterior horn cells is more or less continuous. But when the extrapyramidal influence is removed, leaving only the rhythmical synchronous discharge of the pyramidal tract, tremor results This may well be the correct hypothesis, although it, too awaits confirmation It would well explain the fact that tremor at rest is so often abolished by voluntary movement, for at that time the pyramidal tract is probably activated by an increased number of nervous impulses which are asynchronous

Conclusions

It appears most likely that (1) the involuntary movements of choreoathetosis are produced by nervous impulses arising in the precentral motor cortex and descending from there via the parapyramidal fibers to subcortical centers from which they are relayed to the anterior horn cells by fibers passing in large measure through the anterior fasciculus of the spinal cord. (2) Intention tremor and tremor at rest are produced by impulses passing from the precentral motor cortex to the anterior horn cells via the pyramidal tract. (3) Choreo-athetosis arises when a circular controlling pathway passing from the precentral motor suppressor area (area 4s) and from area 8 to the caudate nucleus and thence to the globus pallidus, to the ventrolateral nucleus of the thalamus, and back to the precentral motor cortex, areas 4 and 6, is destroyed in the caudate nucleus, or less commonly in the thalamus or even the globus pallidus. (4) Intention tremor develops when a circular controlling pathway, which passes from the precentral motor cortex to the pons, the cerebellar cortex, the dentate nucleus, through the red nucleus to the contralateral nucleus of the thalamus and thence back to the precentral motor cortex, is destroyed in the dentate nucleus, the dentato-rubro-thalamic fiber bundle, or in the

thalamus. (5) Hemiballismus arises when a controlling pathway passing through the subthalamic nucleus of Luys is destroyed, but its connections are unknown. (6) Tremor at rest is associated with multiple subcortical lesions, though those in the substantia nigra appear to be the most consistently present. Such tremor may develop because of interruption of a circular controlling neural mechanism which passes from the precentral motor cortex to the substantia nigra, globus pallidus, ventrolateral nucleus of the thalamus, and thence back to the precentral motor cortex. Or, as postulated by Benda and Cobb, it may appear when asynchronous extrapyramidal nervous impulses fail to reach the anterior horn cells, leaving the field clear to a rhythmical synchronous discharge from the pyramidal tract.

Chapter XVI

CLINICAL SYMPTOMATOLOGY

Charles D. Aring, M.D.

Professor of Neurology
University of Cincinnati
College of Medicine
and
Director of the Neurological Service
Cincinnati General Hospital
Cincinnati

OUTLINE OF CHAPTER XVI

Clinical Symptomatology

CLINICAL SYMPTOMATOLOGY

ANALYSIS OF FUNCTION has depended often on painstaking observation of persons suffering from disease by those equipped to deduce the underlying physiopathology. The substantiation of clinically gained information by tissue study considerably enhances its value This method often has had precedence in the resolution of problems surrounding the function of the cerebrum, and it retains a certain value despite extensive experimentation with lower orders of life.

Unfortunately for those with restricted vision, but agreeably for the imaginative and alert clinician, disease does not cut like a knife. It ramifies rather irrelevantly in many instances; from a center of maximum damage it graduates irregularly. A reasonable clinical analyst must consider this fundamental precept of pathology, together with the fact that the signs of disease may be modified by many factors, among the most important being the general physical condition and the personality, to speak very broadly. Difficulty is added to clinical analysis of nervous disease because of the reverberation of effects in an organ as intricate and as exquisitely integrated as the nervous system.

In human pathology, cases suitable for the illumination of the function of the precentral motor cortex are rare. When the lesions are limited more or less strictly to those produced by disease without benefit of surgical analysis (cortical exploration by electrical methods, and excision), and proven by adequate histological study, they approach uniqueness. Obviously this clinical method, when considered alone, will not go far toward elucidating function of the precentral cortex. It would seem redundant to note that the information contained in this chapter on the clinical symptomatology of the precentral region is definitive only in so far as it may be correlated with the substance of other chapters of the monograph, particularly those concerning stimulation and extirpation of the cortex in man (Chapters XIII and XIV).

Noxae, to which may be attributed the ability to affect or destroy precentral cortex in a focal manner, might include trauma, circulatory disturbance, invasion (parasites), infection, toxins, degenerations, and tumor Several of these agents may be summarily dismissed from consideration Vascular pathology, the single most instructive disorder in the field of clinical neurology, is not helpful in this instance The gross circulation usually is not arranged convenient to this study for a single artery supplies more than one architectonic field in the frontal lobe, or more than one large vessel cares for a single area.

Infections and toxins rarely involve the brain locally, and if they do, usually they are not demarcated according to architectonic fields of the cortex. Poliomyelitis might be considered an exception, since the cells of area 4 are rather exclusively damaged so far as the cerebral cortex is concerned. There is, however, so much concomitant involvement of roof and brain stem nuclei, anterior horns, and even sensory mechanisms that a clear analysis of the physiopathology of poliomyelitis remains to be made.

Invasion of the nervous system by parasites is so rare that it barely merits mention.

Degenerations, a term which blankets lack of knowledge, conceivably are pertinent to the subject. Amyotrophic lateral sclerosis might be thought to illustrate the clinical symptomatology of the precentral cortex since it has been considered to attack the pyramidal nerve cells of the precentral cortex rather selectively. Amyotrophic lateral sclerosis cannot be relied upon to elucidate central symptomatology since it is a disease which may involve all of the white matter of the cord except the posterior columns, as well as motor and other nerve cells of the spinal cord and brain stem, besides the precentral cortex. Moreover the pyramidal cells of Betz appear to be involved in only about one-third of the cases (Davison, 1941), and in these, not evenly. (See Chapter XVII.)

Cases of congenital spastic paralysis may occasionally furnish a lead when local cortical atrophy ensues. Great caution must be used in the interpretation of frontal lobe signs in children. It is well known that signs of neurological disease deviate from the usual in infants and children, depending on the stage of development reached by the nervous system at the time that damage occurred. The signs may differ from time to time before they become stabilized. Remarkable compensation for neural deficits may ensue in the young, as has been observed frequently in humans (Marquis, 1935) and animals (Kennard, 1940). There are other drawbacks to accurate interpretation of the causes of the signs of infantile spastic paralysis, among which not the least are the conjunction of lesions which occurred before and after birth and the fact that lesions of recent vintage are seldom subjected to complete neuropathological study.

We are limited in this clinical analysis of the precentral cortex in man (excluding electrical stimulation and excision) to verified, local lesions chiefly produced by trauma or tumor. As a rule, in the former the skull must have been pierced, as by a shell fragment; in the latter the lesion must of necessity be relatively benign. This presentation deals particularly with the symptoms before (convulsions) and after the period of neural shock (diaschisis), if the latter is a consideration. In other words, cases particularly considered are those that have become relatively stabilized or defined.

Syndrome of Area 4 [see *Frontispiece*]

The initial clinical symptom in a local lesion of the area immediately anterior to the Rolandic fissure may be focal weakness, or Jacksonian focal seizures beginning in the face, thumb and index finger, or in the great toe. Motor Jacksonian fits may be brought about by pathological processes causing irritation and sudden discharge of motor elements of the precentral convolution of one side in the first instance. The march of the convulsion most often extends quickly over the entire contralateral half of the body; it may be localized in one limb only or part of a limb, or confined to face and neck; frequently it crosses to the other side before leaving the first. As a rule, convulsion dies out quickest in the segment first concerned and from other parts in the order of their invasion. The frequency of partial fits varies enormously at times. They can become almost continuous (epilepsia partialis continua). Jacksonian fits may be the sole sign of a focal lesion, and their recession may be followed by local weakness or paralysis (Todd's paralysis) and numbness.

Since the anterior central convolution is composed of a large number of foci for movements of the extremities and of the trunk and head, it follows that circumscribed lesions in this area may produce contralateral, focal weakness or paralysis. Thus femoral, brachial, or facio-glossal paralysis or paresis following lesions of the superior, middle, or inferior third of the anterior central convolution respectively have been described. Bilateral paralysis of the feet has followed injury to the paracentral lobules from a shell fragment. Cases in which the fingers of one hand, or one or two fingers were paralyzed have been recorded by several observers. An isolated paralysis of the thumb has occurred in circumscribed lesions of area 4. Foerster (1931) described a patient who had Jacksonian fits always beginning with extension of the fingers, chiefly the fourth. She was unable to adduct the fourth finger, the defect resembling paralysis of the ulnar nerve. The electrical excitability of all of the interossei was normal. At operation, three tuberculomas, not larger than the head of a needle, were situated in the motor area of the fingers at the anterior border of the anterior central convolution.

It is worth stressing that localized lesions in area 4 are capable of producing quite localized paralysis contralaterally, which may resemble the weakness in peripheral nerve lesion. A shell fragment in the face region of area 4 resulted in permanent paresis of the muscles supplied by the inferior branch of the facial nerve. The tongue, mandible, and soft palate were not involved. The paralysis of the external pterygoid muscle as the only sign of trauma to the inferior border of the anterior central convolution has been recorded (Foerster, 1931). Buey has noted paralysis of the

musculature of the thumb and the first and second fingers subsequent to a lesion of area 4. Atrophy is a usual concomitant of this form of cerebral palsy.

One of the more striking deficits following lesions of area 4 is the contralateral loss of isolated movements. Movements of the proximal joints are the least disturbed, and the more complex, learned movements of the distal joints are the most profoundly affected. There is correlation between cortical motor representation for a given muscle group (see the Penfield and Boldrey homunculus, fig. 124) and the degree of paralysis that follows injury to area 4. The cortical representation for the shoulder is relatively small, whereas the representation of the digits occupies a considerably larger area of cortical surface. After damage to area 4 involving a rather large number of foci, the patient may never regain dexterity of finger movements, though he may be able to open and close the hand and the gross movements about the shoulder be relatively efficient (Foerster, 1936a, b). Presumably isolated volitional movements in man depend on the integrity of the nerve cells in area 4, as they most certainly do in the lower forms (Denny-Brown and Botterell, 1938; Dusser de Barenne and Zimmerman, 1935; Hines, 1937; Tower, 1935).

Fig 124—A homunculus illustrating the extent of the motor and sensory representation of various members in the central sector of man (Penfield and Boldrey, 1937)

Focal cortical palsies may be more or less transient. Restitution may be attributed to the rather diffuse representation of any single movement in the pre-Rolandic cortex

In man, in contradistinction to the lower primates, other clinical neurological signs of area 4 lesions are not clear. The lesions which affect area 4 in man usually involve adjacent fields, such as a portion of area 6 or the posteriorly lying sensory fields (figs 2, 3, pp 11-12). The Babinski response is a rather constant phenomenon (Foerster, 1936b; Fulton and Keller,

1932). "Hypotonia" which results from lesions of area 4 in the lower primates is rarely seen in cortical lesions in man, except as an initial effect. Lesions of the postcentral convolution in man have been thought to result in permanent "hypotonia" and atrophy (Head, 1918; Head and Holmes, 1911); the reported cases show evidence of damage close to the central sulcus. It is conceivable that impingment on area 4 may be responsible for the flaccidity, although interruption of the long association fiber tracts from the posterior cerebrum might be indicted without much evidence.

It is not unusual to find sensory deficit in lesions limited to the precentral cortex This is true particularly after acute insult. Usually sensation improves gradually if the lesion is not progressive in nature.

Unlike the result in the subhuman primate when a portion of area 4 is involved, or if the lesion is confined primarily to area 4, the deep reflexes finally are always increased, as usually is the resistance of an affected limb to passive movement after the period of neural shock has passed.

Area 4a—Lesions limited to area 4a or 4s of man are unknown. Excisions involving this portion of the cortex have been done, but they have encroached on other cortical areas. Clinical elucidation of the function of these areas in man depends on studies utilizing stimulation, in which the precentral convolution has been explored consecutively (Chapter XIII). Utilizing this method, it seems clear that the closer one approaches to area 4γ, the more does the result resemble that obtained from area 4γ itself, while the more anterior exploration yields results resembling those obtained from more anteriorly placed cortical fields.

Syndromes of Areas 6 and 44 [see fig. 111, p. 330]

Area 6—There is considerable discrepancy between the ideas of the various students of the frontal lobe about the symptomatology in man of lesions relatively limited to area 6. Fulton and his coworkers, perhaps conditioned by their study of extirpations in monkeys and chimpanzees, have found pertinent similarity between the symptoms of premotor damage in man and of lower primates. Foerster, whose profound experience with cortical physiopathology in man always must be reckoned with, has recorded signs and symptoms of premotor deficit relatively dissimilar to those described for monkeys and chimpanzees.

There is agreement on the form of the seizure produced from area 6. Foerster particularly has pointed out that the Jacksonian seizures produced by lesions of area 6 tend to be "adversive" in type, especially if the pyramidal tract has been interrupted by longstanding disease. In this type of convulsion, head and eyes are turned to the opposite side, the trunk

rotates to the opposite side, the contralateral arm and leg show complex sustained movements of all segments, and there results a tonic-clonic, mass convulsion of all muscles together. In some cases the head and eyes move first, possibly due to the proximity of the lesion to area 8, the trunk follows, and then movements of the extremities occur. In other cases all of these movements appear more or less simultaneously. In a few, the arm begins the movement, rarely the leg. Foerster has called this attack the adversive convulsive fit.[1] Sharply focal seizures beginning with a single movement denote a lesion near the Rolandic sulcus, obviously affecting the cells of area 4. In contradistinction, the convulsive movement produced from area 6 is complex.

With destructive lesions confined to area 6, Foerster (1936b) noted slowness of movement of the contralateral extremities, and difficulty in turning head and trunk to the opposite side. Rapid alternating movements were performed poorly, though isolated, single movements were normal Complicated movement, as is necessary for sequential acts, was affected It is significant that these signs disappear rapidly after ablation of area 6 in man. According to Foerster, the failure of an "extrapyramidal" area in the frontal lobe is compensated for rapidly by other "extrapyramidal" areas in the parietal and temporal lobe, which appear to have the same function to some extent.

Since Bruns (1892) described ataxia in lesions of the cerebrum, particularly of the frontal lobe, many cases have been recorded of verified frontal lobe lesion producing signs which previously had been thought to be indicative of disease of the cerebellum. Thus, Frazier (1936) noted "signs of ataxia" in thirteen of fifteen cases of meningioma occupying the superior lateral surface of the hemisphere anterior to the fissure of Rolando. The signs were bilateral in nine instances, contralateral in three, and ipsilateral in one. He noted one or more of the following signs in 49 per cent of patients with frontal lobe tumor; staggering gait, Romberg sign, dyssynergia, difficulty in performing rapid alternating movements, dysmetria, and nystagmus. These signs, resulting from frontal lobe lesion of one side, may be bilateral or of irregular distribution in the four extremities, and it has been thought that strict unilaterality of these manifestations speaks for a cerebellar rather than cerebral lesion.

Foerster (1936b) did not observe classical cerebellar signs in lesions limited to area 6, although for a few days after unilateral excision of this

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[1] It is appropriate to give Foerster's (1936d) exact description "Dis das Feld 6ₐ ein *Richtfeld* ist, welches den Korper und seine Teile nach der Gegenseite einstellt, indem durch seine Tatigkeit Kopf, Augen und Rumpf nach der Gegenseite gewendet werden, geht ja aus dem Effekt der elektrischen Reizung wie aus dem Geprage des von diesem Felde ausgehenden epileptischen Krampfanfalles unmittelbar hervor Ich habe dis Feld daher schon 1922 als frontales *Adversivfeld* bezeichnet."

area, patients inclined or fell toward the contralateral side and backwards. In Foerster's cases of frontal ataxia, observed particularly in widespread frontal tumor, it is remarkable that ataxia disappeared with excision of the area involved. Obviously the integrity of area 6 is not the *conditio sine qua non* for normal equilibratory function of the cerebral cortex. The destruction of this area will be compensated for sooner or later by the activity of other healthy neural structures. This is a possible explanation for the absence of frontal ataxia in many instances, particularly where the lesion develops slowly.

In lesions of area 6 past pointing may occur, or an extremity may wander toward the side of the lesion. This phenomenon may be present in one arm but not in the other; usually one finds deviation of the contralateral arm toward the side of the lesion and sinking of the same arm. The contralateral leg may cross in front of the other in walking, and in this case the ipsilateral leg deviates outward to avoid the crossed foot. These findings are not seen in all cases.

It is worth repeating that the deficit of slowly produced lesions of area 6 may be extremely meager.

In considerable contrast to Foerster's record of human premotor symptomatology (area 6) and in harmony with their findings in lower primates stands the case recorded by Kennard, Viets, and Fulton (1934). Their patient was a man, 34 years of age, who had an astrocytoma which was limited grossly to area 6 and the upper portion of area 4 of the right frontal lobe.

Signs which appeared to be those of deficit of the premotor cortex were focal seizures of four years duration; the head and eyes turned involuntarily to the left, and the left arm shook, though rigid and drawn up against the body. Unconsciousness then supervened. In later attacks, the left leg was involved in the sustained contraction and shaking. There had occurred increasing awkwardness and stiffness of the left arm, and the patient became unable to use it for delicate manipulations, though a powerful grip remained. For six months before operation he had been unable to release the grasp of the left hand, and he had ceased using it since such effort was likely to bring on a seizure. For nine weeks before operation, the left hand was redder and warmer than the right hand, and at times it swelled for periods of an hour or two.

On examination, the patient showed weakness of the left arm, particularly in the grip. The deep reflexes were slightly more active in the left extremities. There was ankle clonus on the left. The plantar responses were flexor in type. Any pressure on the flexor surface of the fingers of the left hand, particularly if it was sufficient to stretch the flexor muscles slightly,

caused strong involuntary grasping. Relaxation was slow and apparently involuntary.

In slowly developing lesions of the premotor area the symptoms *may* follow a distinct chronological pattern. Generalized weakness of the contralateral extremities, especially of the grip, appears early. At first, this may be manifested by inability to perform skilled movements, particularly with the digits, without much demonstrable impairment of the motor power. The patient, however, may complain of local weakness despite the inability of the physician to demonstrate it. It should be remembered that "objective" tests for motor loss are among the crudest in neurology and that the patient's word in this instance usually is better evidence than the physician's impressions.

With the lesion of area 6 that develops in a gradual manner, contralateral spasticity with increased deep reflexes, the sign of Hoffmann,[2] forced grasping, and vasomotor disturbances appear late. When well developed, the spasticity of a premotor lesion resembles that occurring in hemiplegia. This spasticity is a state of sustained contraction of the antigravity groups of muscles which may vary in degree from patient to patient. When the muscle is passively stretched, it resists to a certain point and then relaxes. If the limb is then allowed to remain in the new position for a moment it holds there like a "clasp knife," whether it be after shortening or lengthening. Associated increase of the deep reflexes may be demonstrated in the fingers and toes (signs of Hoffmann, Rossolimo, and Mendel-Bechterew[3]).

It is thought that contralateral fanning of the toes may occur on testing for the plantar response after premotor lesions. Exaggerated plantar flexion of the toes has been recorded.

The grasp reflex may appear late in premotor lesions. It is elicited by stimulating the skin of the palm of the hand with a long object (e.g. the handle of a reflex hammer), stroking distally. Toward the end of the

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[2] This reflex may be elicited by snapping the terminal phalanx of a finger, usually the second, in such a manner as to bring about a sudden brief pull upon the flexor muscles. If the Hoffmann response is positive the fingers and particularly the thumb describe a reflex movement of flexion. The subject's hand must be reasonably relaxed, sometimes it is advantageous that the finger flicked be hyper-extended and at other times this finger is better semi-flexed. Both attitudes of the stimulated finger should be tried. The Hoffmann sign (Wartenberg, 1945) may occur with involvement of the cortico-spinal tract to the upper extremity, however, it may be seen in persons who are intact neurologically and who have hyperactive deep reflexes. The Hoffmann sign is to be considered indicative of pyramidal tract lesion only if elicited unilaterally, or if it is of unequal intensity in the two hands, or in the presence of other indubitable evidence of pyramidal tract involvement.

[3] The sign of Rossolimo consists of plantar flexion of the toes, induced by a sudden pull on the flexor muscles. The sign may be tested by flicking the toes dorsalward, by a light tap of the examiner's fingers. The sign of Mendel-Bechterew is elicited by tapping the dorsum of the foot, usually the cuboid bone. Plantar flexion of the toes results exactly as is the case in the Rossolimo response.

maneuver, the flexor muscles of the finger are put on a slight stretch. If the grasp reflex is present a powerful flexion of the fingers ensues which the patient relaxes slowly and with difficulty. The reflex is exaggerated if the subject reclines in the lateral recumbent posture with the affected extremity uppermost, and is diminished when he lies with the affected extremity nethermost. When the clenched hand is empty or if it is actively or passively closed, voluntary relaxation is easy. It is sometimes difficult to evaluate the grasp reflex, particularly when the patient is not alert. If the response contains considerable volition in its make-up, it may be found that the grasp will release early despite the maintenance of pressure on the flexor muscles. Another method of evaluating the response is to request the patient who is able to cooperate to release the grasp. If he is unable to do so promptly, the response might be considered to be of reflex origin. The grasp reflex may be demonstrable in the foot contralateral to the cerebral lesion.

These grasping movements appear to be analogous with those met with in infants. The movements of the learning period become less automatic and more voluntary as motor patterns are acquired which supplant the inherent reflexes. Conversely the loss of the former may uncover grasping movement which seems more or less automatic in nature.

The grasp reflex has been noted with lesions of the brain located in regions other than the frontal lobe. It is noteworthy that Foerster (1936b) never observed any trace of the grasp reflex in any case of destruction of areas 6 or 4, or a combination of the two.

The reports of Wilson and Walshe (1914), Walshe and Robertson (1933), Adie and Critchley (1927), and Kennard, Viets, and Fulton (1934), and others contain descriptions of patients with forced grasping, in whom the locale of the lesions as verified at operation or autopsy was the posterior part of the frontal lobe, just anterior to area 4.

Vasomotor changes, such as edema or vasodilatation, in hemiparetic limbs are well known. Evidence is meager in the clinical literature (Kennard, Viets, and Fulton, 1934) to complement the studies in subhuman primates, in which it appears there is always a change in skin temperature in the contralateral extremities following lesions of the premotor areas (Kennard, 1935). Recently Bucy and Pribram (1943) have noted localized paroxysmal attacks of sweating in association with a tumor underlying the lower part of area 6 and area 44.

Psychic changes have been reported associated with disease of area 6, consisting of emotional instability, change in character, confusion, or slowing of mental activity. Mental signs can hardly be of localizing value, since they appear with lesions of many portions of the cerebrum.

Area 44—Foerster has recorded lesions in area 44 (his area 6b) which caused attacks of mastication, licking, swallowing, grunting, and croaking, and in one case rhythmic singultus followed by masticatory and licking movements and then a typical Jacksonian fit. Abnormal sensations of the larynx, pharynx, and mouth may precede the motor phenomena. Foerster noted a special form of pseudobulbar palsy, the substratum for which was a lesion in area 44 of one hemisphere. The patient had difficulty in the control of the face, tongue, jaw, palate, and vocal cords. Movement was intact, but when speech was attempted dysarthria or even anarthria was the result. Consonants were pronounced with greater difficulty than vowels. in severe cases, speech was inarticulate; the difficulty was not in dropping or adding words, but in the sequence of sounds in words; the change from one sound to the next was difficult, particularly if several consonants were close together. In one instance, a man with a subdural hemorrhage on the left was thought to have tetanus because of inability to move the jaws or to speak. Reference should be made to the excision and electrical stimulation of this area (Chapters XIII and XIV) for further information.

Lesions of area 44 and areas immediately neighboring may cause apraxia. This is a defect in rapid and rather automatic performance in response to a command, and is often associated with loss of psychic elaboration (eupraxia) necessarily a precursor to initiating any motor act. In most instances this latter function is bilateral—the performance of one hand is planned in the opposite precentral and supramarginal gyri.

Apraxia of the larynx, tongue, and lips causes expressive aphasia, and the patient is no longer able to make the movements of articulation, even though he may know exactly what he wants to say. This is hardly the place for a consideration of the complexities of the disorders of speech (aphasia), which merit mention because of the importance of the inferior portion of the precentral cortex in the control of its organs. Reference may be had to the writings of Nielsen (1946) and others for aid in understanding disturbances of language.

Syndrome of Area 8 [see Frontispiece]

On irritation of this precentral cortical area (during convulsion) the eyes turn to the opposite side; occasionally the eyes may turn toward the opposite side and upward, and very rarely downward. The head does not participate in the reaction, if the disturbance remains local. In a convulsion the eyes are turned by a series of clonic twitches to the opposite side; then the movement may become tonic. The attack may be limited to

the eye muscles, but in most cases it spreads to involve adjacent cortical areas (6 and 4). When the stimulus spreads, the eye movements are accompanied by turning of the head and trunk to the opposite side and by sustained movement of the contralateral extremities, as described in lesions of area 6. If the stimulus spreads to area 4, clonic twitches of the contralateral side of the face, neck, and of the fingers may be expected, and thence possibly of the entire musculature of the extremities. Such a fit naturally might be confounded with one originating from area 6 unless the evolution of the attack is observed closely.

With destructive lesions of area 8, one may expect to find deviation of the eyes toward the side of the lesion and inability to move the eyes to the contralateral side or, on the other hand, there may be no demonstrable disability of the eye movements. This factor probably depends on the acuteness of the lesion; acute lesions might be paralytic while those of slower evolution might be readily compensated for by other cortical eye-turning centers. (See Chapter XII for a fuller discussion of this area.)

Combined and Bilateral Lesions

Obviously the deficit is worse with simultaneous or sequential involvement of more than one area of the cortex. With combined lesions, one may expect any of the symptoms previously described in this chapter to be accentuated, and to be enduring rather than to recede as the stage of their inception passes.

There is no reliable information on the simultaneous or sequential involvement by disease of one or more of the precentral cortical areas on both sides. The reader is referred to the surgical consideration of these matters (Chapters XIII and XIV).

Summary

An essay which attempts to break down the clinical symptomatology of the precentral cortex cannot be definitive. Possibly the exploitation of electroencephalography will assist in the task in the future. This field is a difficult one, for here anatomy, physiology, psychology, psychiatry, and neurology have exerted their influence, and the conglomeration of data is particularly difficult of analysis and presentation. Indeed, clinically there is little reason for doing so. A consideration of the basis of the matter—the complex anatomical feltwork, the connections of which extend far beyond the limitation of the precentral area, in fact to the frontal pole and far back into the sensory areas, as well as to the numerous subcortical gray structures—at once indicates the futility of attempts to break down the

function of the precentral region accurately. There is a peculiar danger in attempting to hold up to view part of a whole in this instance as in many another.

It should be remembered that symptoms sometimes seen in precentral lesions are not specific, for many of them may be seen with disease in areas other than the frontal cortex. For example, ataxia has been described with lesions involving other cortical and subcortical areas than area 6, as has been "forced grasping." Clinical neurologists know full well that one or two signs of themselves may have little localizing value except when they correlate with the entire picture.

From a clinical standpoint it is more useful to indicate the signs that may be present in disease of the frontal lobe, many of which have been described in the foregoing discussion. The syndrome of the frontal lobe may show such variance from patient to patient, as to be no syndrome at all. Every neurologist can recall a patient with a large unilateral frontal glioma whose only symptoms for months up to the day of operation were facetiousness and other milder mental signs; or the symptomless case with a large frontal lesion revealed at the autopsy table.

The gamut of mental symptoms has been described in association with frontal lesions. While we are well aware that mental signs are not signs of cerebral localization, the apathetic, slovenly, indifferent, uninhibited, facetious, euphoric individual has been seen with enough frequency in association with frontal lobe disease to form a constellation in the minds of most neurologists. Reflex sucking is usually looked for, and also the grasping and groping which has been so thoroughly analyzed by Walshe and Robertson (1933); it should be obvious that the function of the first and second cranial nerves must be thoroughly analyzed, since they are readily impinged upon by space-consuming lesions of the frontal lobes. Extremely mild differences in motor performance are carefully searched for in the face and extremities; one portion of the anatomy is, as always, compared with that of the opposite side. Unilateral diminution or absence of the abdominal skin reflexes weighs heavily in the consideration of some physicians as an indication of frontal lobe localization.

To repeat, any of the symptoms and signs generally associated with frontal lobe disease may be seen in disorders of other parts of the brain. Frontal lobe symptoms and signs vary according to the speed of development of the lesion and other unknown factors, which most likely relate particularly to the personality development, but also to complex anatomical connections as yet not clearly elucidated.

The complexity surrounding a reasonable analysis of cerebral lesions was enunciated by Hughlings Jackson and summarized by Broadbent (after Walshe, 1942) as follows·

"The functions of a centre in which a lesion has occurred are suspended, and corresponding symptoms may be called negative. These are, however, not the only symptoms; others, usually more obtrusive, and often infinitely more important, are produced by the activities of other centres, either (1) unbalanced in consequence of the absence of normally opposing activities; or (2) liberated from the control of higher level centres; or (3) intensified by attempts to compensate for the missing function."

Chapter XVII

PATHOLOGY

Charles Davison, M.D.

Neuropathologist and Attending Neuropsychiatrist
Montefiore Hospital
and
Consulting Neuropathologist
Beth Israel Hospital
New York

OUTLINE OF CHAPTER XVII

Pathology

PATHOLOGY

THE PRECENTRAL MOTOR CORTEX consisting of areas 4, 6, and 44 of Brodmann (see Chapter II) is the seat of numerous physiological functions. Pathological states in these areas result in numerous neurological symptoms and signs. Outstanding among these are disturbances in muscle tonus—flaccidity and spasticity—alterations in the deep and superficial reflexes, disturbances in volitional skilled movements and behavior, focal or Jacksonian seizures, forced grasping and groping, and autonomic, extrapyramidal, and ocular disturbances.

Although pathological lesions are seldom strictly limited to single areas in the cortex, there are, nevertheless, disease entities which involve these restricted areas. A syndrome or disease involving areas 4 and 6, or at least their efferent connections, is amyotrophic lateral sclerosis. In addition, there are a number of diseases of the central nervous system, such as tumors or vascular insults, which may affect the above areas and lead to symptoms which are directly attributable to their involvement or to involvement of their afferent and efferent connections. There are also a number of extrapyramidal disorders in which some of the symptoms could be correlated with implication of the above structures. Clinicopathological cases pertaining to these disorders, despite their limitations, will be used to illustrate the functions of these various areas. As areas 4, 6, and 8, as well as their projection fibers, lie close together (see frontispiece and fig. 63, p. 137), and since disease seldom affects one area alone, these areas, especially 4 and 6, will be treated together.

As already stated, a disorder that affects these regions or their projection system is amyotrophic lateral sclerosis. The gross atrophy of areas 4 and 6 in this disorder was first observed by Kahler and Pick in 1879. Kojewnikoff (1883) was the first to trace the degeneration of the pyramidal tract from the motor cortex into the internal capsule, peduncles, pons, medulla oblongata, and spinal cord. Charcot and Marie (1885), who confirmed Kojewnikoff's observations, also demonstrated the disappearance of the giant pyramidal cells from area 4. Sarbo (1898), Rossi and Roussy (1907), Probst (1903, 1906), Campbell (1905), and Spiller (1905) in further contributions stressed the involvement of area 4; Rossi and Roussy, Probst, and Campbell showed that area 6 was also partially implicated in this disease. In many instances of amyotrophic lateral sclerosis as demonstrated by Marie (1928), Dercum and Spiller (1899), von Czyhlarz and Marburg (1901), Bertrand and van Bogaert (1925a, b),

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Neri (1925), and Davison (1941), the degeneration could not be traced higher than the brain stem. Although Davison and others have shown that this disease of the upper motor neuron originates in the giant pyramidal cells of Betz of area 4 in only about one-third of the cases, nevertheless, the resulting symptomatology will be similar no matter where the projection fibers of areas 4 and 6 become involved. The cases of amyotrophic lateral sclerosis used in this presentation will be confined to those in which both the cortical areas and their respective fiber tracts were involved.

There is no doubt that the corticospinal projections in man and other primates originate largely from the precentral convolutions. Holmes and Page May (1909) were of the opinion that the pyramidal tract had its origin solely from the giant pyramidal cells of Betz in area 4. These conclusions were based on experimental studies of the cerebral cortex following lesions of the spinal cord in which retrograde changes were found in the Betz cells. Schröder (1914), Minkowski (1923-1924), and von Economo and Koskinas (1925) found evidence of retrograde degeneration in the large pyramidal cells, not only in area 4 but also in area 6 following spinal lesions. Levin (1936) believed that when present, such retrograde changes in area 6 are restricted to heterotopic giant pyramidal cells of Betz. Further proof that the pyramidal tract fibers must originate in other areas beside area 4 is the fact that Campbell (1905) estimated the total number of Betz cells in each hemisphere of man as 25,000, while the total number of fibers in each pyramidal tract entering the spinal cord on one side is about 1,000,000 (Lassek and Rasmussen, 1939). Furthermore, Penfield and Erickson (1941) have shown that only 3 per cent of the pyramidal tract fibers arise from the giant cells of area 4. According to these authors, the giant cells do not represent a physiological group, but only the largest members of a much more numerous group of pyramidal cells (see also Chapters V and VI). The prevailing opinion is that cells other than the Betz type give origin to a large percentage of pyramidal tract fibers.

Spasticity, Flaccidity, and Alterations in Reflexes

Spasticity—It is generally accepted that spasticity or exaggerated reflexes occur when there is involvement of areas 4 and 6 or their projection system. Although any lesion of these areas or their descending pathways may cause these neurological signs, disease entities which illustrate this best are amyotrophic lateral sclerosis and vascular insults limited to areas 4 and 6 or to the internal capsule. Illustrative cases of each will be given. The interpretation of clinical and pathological findings resulting from involvement of the bulbar nuclei and anterior horn cells in amyotrophic lateral sclerosis will be omitted.

CASE 1

Amyotrophic Lateral Sclerosis

R A, a man aged 53, developed progressive weakness of the legs so that he finally was unable to walk without the aid of a cane There was a gradual progression of symptoms with extension of the process to the upper extremities The symptoms referable to the cranial nerve nuclei and anterior horn cells are omitted

Neurological Examination — Examination of this patient disclosed the following spastic gait with spasticity in all the muscles including those of the upper extremities, marked fibrillations and atrophies of the muscles of the lower extremities, shoulders abdomen, and back, weakness in the extensor muscles of the legs and inability to perform skilled or purposeful movements, clumsiness in the execution of volitional movements, hyperactive reflexes throughout involving both lower and upper extremities, presence of abdominal and cremasteric reflexes, positive bilateral Hoffmann, Babinski Oppenheim Mendel-Bechterew and Rossolimo signs

Autopsy Report — The outline, especially of area 6, could hardly be made out The gray matter of area 4 was narrower than normally There was a distortion in the arrangement of the cytoarchitectural layers of areas 4 and 6, especially of area 6 A number of the pyramidal cells had a shadow-like appearance The giant pyramidal cells of Betz were diminished in number and showed pathological changes —such as chromatolysis, shrinkage pyknosis, and severe cell changes The internal capsule and peduncles were slightly pale and showed disintegration of myelin sheaths and axis cylinders, these changes were more distinct in the Sudan III and Marchi preparations The pyramids of the pons and medulla oblongata were demyelinated and showed more extensive pathologic changes than the internal capsule and peduncles

In the *spinal cord* there was extensive demyelinization of the crossed and direct pyramidal tracts throughout all segments The myelin sheaths and axis cylinders were severely damaged

This case illustrates many signs which occur with lesions in areas 4 and 6. The spasticity, the exaggerated reflexes, and the positive Hoffmann, Babinski, Rossolimo, and Mendel-Bechterew signs were caused by the lesions in areas 4 and 6 or their descending pathways. In this instance, the pyramidal tract was involved throughout its course, but particularly in the brain stem and spinal cord

Fulton and his co-workers have demonstrated that when area 4 alone is removed in monkeys and chimpanzees exclusive of the strip region (area 4s), there develops a paralysis which is first flaccid in all joints but which later passes through a stage of transient spasticity of digits, ankle, and wrist. When area 6, including the strip or area 4s (Hines, 1937), is also ablated, the previously flaccid extremity becomes highly spastic and remains so. It is believed that the intensity and duration of spasticity are functions, not of any one area, but of the extent of interruption of the extrapyramidal cortical projection. Tower and Hines (1935) further observed that primary section of the pyramids in monkeys causes flaccidity instead of spasticity. This, apparently, is not true in the human, for observations of cases of amyotrophic lateral sclerosis with lesions of the pyramids beginning in the medulla oblongata, still showed spasticity (Davison). Furthermore, destruction of the pyramidal tract in these

areas in other diseases also resulted in spasticity. When, however, there was additional involvement of the medial lemniscus or cerebellar pathways, the resulting paralysis was flaccid (fig. 125). In this case of infarction of the medulla oblongata, the entire right pyramid in the medulla oblongata was affected. The paralysis, however, was flaccid in type, probably as a result of involvement of other pathways in the medulla oblongata

On the basis of their experiments, Fulton and his co-workers concluded that in monkeys and chimpanzees spasticity results from the removal of

Fig 125—Infarct of the medulla oblongata involving the right pyramid, medial lemniscus and the greater part of the inferior olivary nucleus and its pathways Flaccid hemiplegia

cortical extrapyramidal control of lower centers According to these authors, the enduring state of spasticity depends upon the extent of the involvement of areas 4 and 6; the greater the involvement, the more marked the spasticity. This cannot be confirmed fully in man, for others and I have reported occasional cases of flaccid hemiplegia with fairly extensive lesions of areas 4 and 6 [1]

Flaccidity—Kennard and Fulton (1933), in their experiments with cortical ablation in primates observed that a lesion restricted to area 4 resulted in a contralateral flaccid hemiplegia Spasticity appeared only

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[1] [Such facts as these clearly demonstrate the difficulties in arriving at sound physiologic conclusions from human cases with spontaneous lesions, particularly those with diffuse alterations as compared with the study of otherwise normal experimental animals in which discrete lesions have been made—Editor]

when area 6 was removed. They concluded that in primates spasticity is present after area 6 has been ablated and fails to appear if that area remains intact. Later, Kennard, Viets, and Fulton (1934) observed a case in which a cystic astrocytoma, restricted to the right premotor area, led to focal seizures, progressive rigidity, awkwardness and stiffness of the left arm, forced grasping, increased reflexes, and vasomotor disturbances. The removal of the neoplasm led to recovery and to a complete flaccid paralysis. Twenty-five days after the operation, persistent spasticity of moderate degree appeared. The authors concluded that in "premotor lesions, awkwardness, spasticity and increase of tendon reflexes appear early, before the onset of motor weakness; whereas, in lesions of the motor area, weakness begins early, reflexes are at first depressed and spasticity, if present, appears late. . . . Acute injuries or rapidly expanding lesions of the motor area produce flaccid paralysis and generalized depression of the reflexes."

Davison and Bieber (1934), from a study of about fifty cases of cerebrovascular diseases with closure of the middle cerebral artery, found that the lower two-thirds of the premotor area became involved. The upper one-third or mesial part of the premotor area is supplied by the anterior cerebral artery. In the series of fifty cases of complete thrombosis of the middle cerebral artery, three were cases of flaccid hemiplegia and the rest of spastic hemiplegia. Three additional cases of flaccidity due to partial occlusion of the middle cerebral artery were also found and included in the group. The degree of premotor implication in the six cases of flaccid hemiplegia was compared with that found in the cases of spastic hemiplegia. The shortest acceptable period for the duration of flaccidity was taken as eight weeks. A number of similar cases have been seen since then.

In order to supplement the studies of involvement of the premotor area and the role it may play in spasticity, cases of closure of the anterior cerebral artery were also reviewed. Obstruction of this vessel, as already mentioned, destroys part of the first frontal convolution and the anterior part of the paracentral lobule which enters into the formation of areas 4 and 6. With one exception, Lhermitte's case, all of the cases of disease of the anterior cerebral artery collected by Critchley (1930) presented spastic hemiplegia. Davison, Goodhart, and Needles (1933) also reported two cases of spastic hemiplegia caused by occlusion of the anterior cerebral artery. However, in one case, described below, occlusion of the anterior cerebral artery resulted in a flaccid hemiplegia. Davison and Bieber (1934), as well as other clinicians, have emphasized that in most cases of flaccid hemiplegia, the sensory cortex or pathways were involved in most or

practically every instance Later, Kennard and Kessler (1940) also noted that flaccid paralysis is apt to be associated with sensory disturbances By ablation of various parts of the sensory and motor cortex, they were able to produce flaccidity. I have also observed a number of cases of flaccid hemiplegia, associated with thalamic and other deep-seated lesions. in which the cortical premotor area was spared.

Cases of occlusion of branches of the anterior cerebral artery and of complete and incomplete occlusions of the middle cerebral artery will be discussed.

Fig 126 (Case 2) —Flaccid paralysis of the right upper extremity as a result of thrombosis of branches of the left anterior cerebral artery with essential involvement of areas 6 and 8 and slight involvement of area 4

CASE 2

Thrombosis of Branches of the Left Anterior Cerebral Artery

R L, a man, aged 73, developed a right flaccid hemiplegia Examination disclosed an anomia, slight mental impairment a complete flaccid paralysis of the right upper extremity with areflexia, absent abdominal and cremasteric reflexes on the right and paralysis of conjugate movement of the eyes to the right The flaccid paralysis persisted for over two months, until he expired

Autopsy Report—There was softening of the left precentral region, area 6 was more involved than area 4 This was best brought out in the horizontal sections stained for myelin sheaths (fig 126) where demyelinization was present at the base of the second frontal convolution and in area 6 The leg region of area 4 on the left was also slightly involved In other

Fig 127 (Case 3)—Horizontal section showing involvement of the second and third frontal, precentral, postcentral, insular and first second and third temporal convolutions following complete occlusion of the right middle cerebral artery Flaccid paralysis, Cresyl violet stain

sections there was implication of area 8 The areas of destruction were filled with compound granular corpuscles and proliferating vessels The cytoarchitectural layers, especially of areas 6 and 8, were markedly distorted with severe destruction of the nerve cells Sections through the internal capsule, pons, and medulla oblongata did not show any descending degeneration

The lesion in this case was most severe in those parts of areas 6 and 8 which are supplied by the anterior cerebral artery. Although area 6 was mostly involved, the resulting picture was one of flaccidity. The paralysis of conjugate movement of the eyes was most likely the result of the lesion in area 8. Despite the lesion in area 6, there was no increase in the contralateral reflexes, and except for absence of abdominal and cremasteric re-

Fig. 128 (Case 4) —Incomplete occlusion of the left middle cerebral artery causing destruction of the white matter from the lower two-thirds of the premotor area Flaccid paralysis

flexes, there were no pathological reflexes such as Hoffmann, Babinski, or Rossolimo, as would be expected with such lesions.

CASE 3

Complete Occlusion of the Middle Cerebral Artery

C A, a man, aged 65, developed a complete left-sided paralysis The neurological examination disclosed a complete left flaccid hemiplegia with motor weakness, exaggerated tendon reflexes, Hoffmann's and Babinski's signs, and impairment of all modalities of sensation on the left side The flaccid hemiplegia persisted for three months, until the patient died

Autopsy Report—There was complete closure of the right middle cerebral artery with softening of the following convolutions second and third frontal, precentral, opercular insular, postcentral, parietal, and temporal (fig 127)

CASE 4

Incomplete Occlusion of the Middle Cerebral Artery

S A, a woman aged 48, had a cerebral episode, after which a right flaccid hemiplegia and aphasia developed Neurological examination revealed severe motor aphasia, right flaccid hemiplegia, right hyperreflexia with Babinski and allied signs, and sensory disturbances on the right side The flaccid hemiplegia lasted seven months

Autopsy Report—There was incomplete occlusion of the left middle cerebral artery with destruction of the white matter of the second and third frontal convolutions and the lower two-thirds of the premotor area (fig 128)

Although the evidence in man is not as conclusive as in the experimental animals, it can be safely stated that flaccidity as well as spasticity has some relation to the premotor region and that, of lesions in areas 4 and 6, those of area 4 most likely result in a flaccid paralysis This was demonstrated in monkeys and chimpanzees by Fulton and Kennard (1934), and by Foerster in man. In most instances, the influence of the sensory cortex on flaccidity cannot be completely eliminated.[2]

Reflex Changes—Experimentally, Fulton and his co-workers have shown that a lesion sharply restricted to area 6 causes transient moderate increase in the contralateral tendon reflexes and the appearance of various signs (Hoffmann and Rossolimo), the changes being more marked in the chimpanzee than in monkeys.[1] When however, area 6 is removed some

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[1] [The fact that in fifty cases of occlusion of the middle cerebral artery, forty-seven had a spastic hemiplegia indicates that destruction of the precentral motor area releases the postural reflexes to a hyperactive state It would seem most likely that in the other three cases with flaccid hemiplegia some additional lesion which was not observed must have prevented the postural reflexes from becoming hyperactive In individuals with cerebral vascular disease such multiple lesions are of course, not uncommon Small additional lesions which might be of physiological significance disproportionate to their size might easily have escaped careful investigation—EDITOR]

[2] [The demonstration by Hines (1937) that the "strip," now known as area 4s, is the portion of the cortex lying anterior to area 4 in the subhuman primates which is primarily concerned with the postural reflexes and the destruction of which results in exaggeration of the myotatic reflexes and the appearance of spasticity has now been confirmed by Fulton and other workers—EDITOR]

months after a lesion of area 4 the reflex changes are more marked and enduring. This is even more true in man, as shown in many of our cases of amyotrophic lateral sclerosis, or in those with extensive vascular or neoplastic lesions with involvement of areas 4 and 6.

The Babinski sign undoubtedly is the result of the lesion in area 4. The Hoffmann sign is possibly the result of involvement of areas 4 and 6 and becomes permanent, as shown in chimpanzees, when both areas are affected. This sign disappears within a few weeks after an isolated premotor lesion. The Rossolimo and Mendel-Bechterew signs become markedly exaggerated with extrapyramidal lesions of the cortex. Rossolimo (1895) originally believed that the exaggeration of this reflex was not caused by the interruption of the pyramidal tract itself, but was the result of impairment of an hypothetical tract under cortical influence which descended along with the pyramidal tract.

Atrophy

Atrophy of muscles in amyotrophic lateral sclerosis is unquestionably the result of involvement of anterior horn cells. This topic would not be discussed at all were it not for the fact that Fulton and his co-workers observed atrophies in the chimpanzee affecting most particularly the distal muscles, following lesions restricted to area 4. They noted in one chimpanzee, that nine months after a lesion of area 4, the muscles on the affected side weighed only one-third as much as the corresponding muscles on the normal side. In another the atrophy was more than 50 per cent. Fulton states that atrophies of this character have not been observed following lesions of any other cortical area, being notably absent after ablation of the postcentral convolutions and other parts of the parietal lobe. They believe that atrophies with sensory disturbances after postcentral lesions are due to encroachment of the lesions upon area 4. I have observed atrophy of muscles with parietal lobe or thalamic lesions in man but never with lesions in areas 4 and 6. Although the atrophies with lesions in area 4 described by Fulton, as far as I know, were not reported by others in man, such a possibility cannot be excluded (see Chapter XIV, pp. 382 and 387).

Volitional and Skilled Movements

Practically every patient with amyotrophic lateral sclerosis or with vascular or neoplastic disease involving the premotor region has some disturbance in volitional and skilled movements. This undoubtedly is the result of the lesion of the pyramidal tract, and in amyotrophic lateral sclerosis, also of the anterior horn cells. In this presentation I shall limit the discussion to the disturbance in movements secondary to lesions of the pyramidal tract.

Experimentally, ablation of area 4 in animals and man results in paralysis of volitional movements, especially of highly organized skilled movements. As is well known, the higher the development of the cerebral cortex, the more marked does this disturbance become, reaching its greatest intensity in man. Apparently the movements most recently acquired in phylogenetic history, such as those of the digits and those most extensively under cortical control, are the ones most severely affected by lesions of area 4.

The chimpanzee (Fulton), after removal of area 4, never regains dexterity of finger movements. Foerster found the same in man. In ablating the leg area of area 4 in the chimpanzee, hip movements are the first to return and toe prehension the last. Denny-Brown and Botterell (1938) found that after partial lesions of area 4 in monkeys individualized movements, especially of the digits, still occurred if any part of the Betz cell area was left intact; such movements disappeared if all Betz cells were destroyed. Kennard has followed the development of baby monkeys in which area 4 had been removed from both cerebral hemispheres Although the animals acquired movement-patterns, finely coordinated and individualized movements of the fingers were never developed From clinical observations in man and from the above experiments, it may be concluded that area 4 is concerned with the performance of volitional and skilled movements.

All the above facts are illustrated by cases of amyotrophic lateral sclerosis and of cerebral vascular occlusion In Huntington's chorea the impairment of skilled movements can be explained on the basis of involvement of the frontal cortex and in some cases of the precentral region. I have seen nine such cases that came to necropsy The brief description of one case will illustrate this point

CASE 5

B N, a woman, aged 35, showed all the symptoms of chorea She dropped objects from her hands and was unable to perform certain skilled acts, except with great difficulty There was a familial history of Huntington's chorea

Neurological and Mental Examinations —The examinations disclosed generalized choreiform, athetotic, and dystonic movements which were aggravated by emotional factors and voluntary acts She was unable to perform simple skilled acts, except with great difficulty All of the deep reflexes were hyperactive and there was a question-

able bilateral Babinski sign There was some weakness of all the voluntary muscles Except for slight euphoria there was no mental change

Autopsy Report—There was slight atrophy of the frontal and precentral region. There was moderate symmetrical hydrocephalus, narrowing of the gray matter and shrinkage of the basal ganglia affecting primarily the striatum (caudate nucleus and putamen) Microscopic sections from the frontal and precentral cortex (areas 4 and 6) disclosed a distortion in the arrangement of the cytoarchitecture (fig

129) There were small areas of devastation with diminution in the number of nerve cells The remaining nerve cells showed many types of pathological changes The changes in areas 4 and 6 were more extensive than in the frontal areas The changes in the basal ganglia were typical of those seen in Huntington's chorea

This case is of interest from several angles. Although clinically this was a case of Huntington's chorea, there were no mental symptoms, except for a slight euphoria. This was in conformity with the insignificant changes in the frontal convolutions and the more severe changes in the precentral area. Most cases of extrapyramidal disorders do not show marked disturbances in the performance of highly skilled acts, except very late in the illness. It is well known that such patients despite their marked involuntary movements are able to perform highly skilled acts such as throwing and catching a ball, playing the piano, or riding a bicycle. This patient was unable to perform even simple voluntary skilled acts, although the involuntary movements were less marked than in the average case of
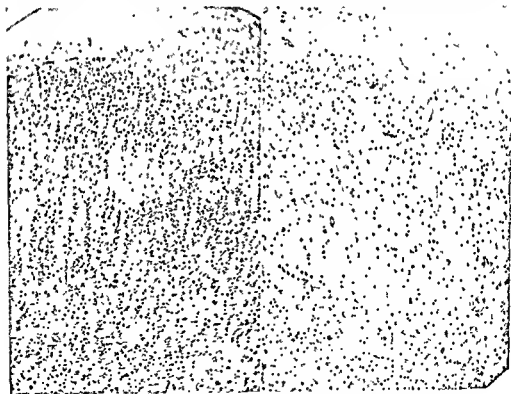
Fig 129a   Fig 129b

Figs 129a-b (Case 5) — Fig 129a   Section from area 6 disclosing distortion in the arrangement of the cytoarchitectural layers and dropping-out of nerve cells and areas of devastation Fig 129b   Section from area 4 showing slight distortion in the arrangement of the cytoarchitectural layers, dropping-out of nerve cells, and small areas of devastation. Cresyl violet x 40

chorea. That the lesions in areas 4 and 6 were responsible for her inability to perform skilled acts is evidenced also by the generalized hyperreflexia and the questionable bilateral Babinski sign.

Behavior Disturbances

Behavior disturbances are rarely seen in amyotrophic lateral sclerosis, and when they do occur, as described by Wechsler and Davison (1932) and others, they are most likely the result of involvement of the frontal convolutions (Brickner, 1936) A number of observers, however, believed that lesions in area 4 may cause disturbances in behavior. Krasnogorski (1909) found that conditioned reflexes to proprioceptive stimulation were permanently abolished in the dogs after removal of the sigmoid gyrus. Jacobsen (1934), by complete bilateral destruction of area 4 in monkeys and chimpanzees, found that immediately after the operation the animal showed serious incoordination in the performances of acts which it was trained to perform prior to the operation (problem boxes) The animals apparently knew what to do but encountered difficulty in executing the necessary movements. Jacobsen was of the opinion that the retention of acquired habit patterns is not impaired by destruction of area 4, although the execution of these complex manipulations may be rendered difficult for a time by virtue of motor weakness. These findings also confirm the results obtained by Rothmann (1904) and Lashley (1924). There is, however, some agreement that the intact motor area gives a smoothness to behavior patterns. The combination of involvement of the frontal convolutions and area 4, as seen in cases of amyotrophic lateral sclerosis with mental symptoms, or in other pathologic states, leads to a great disintegration of the smoothness of behavioral patterns. The following case illustrates this point.

CASE 6

Amyotrophic Lateral Sclerosis with Mental Symptoms and
Disturbances in Behavior Pattern

H. L., a man, aged 38 presenting the typical manifestations of amyotrophic lateral sclerosis, first experienced impairment of memory He made statements without being aware of what he said; he could not recall the names of his parents and failed to recognize the members of his family, or the house and street on which he lived He was unkempt, unconcerned, and could not perform simple skilled acts At times he walked about without clothes and urinated in an appropriate places He was unable to maintain sustained attention.

Neurological and Mental Examinations —In addition to the typical findings of amyotrophic lateral sclerosis, examination disclosed that the patient's speech was limited to monosyllables; he tended to perseverate and answered "yes" to his name repeatedly He had difficulty in unbuttoning his coat, removing his clothes, lighting a cigarette, combing his hair, writing, etc He was disoriented for place and persons He wandered aimlessly about the ward, smiled fatuously and reacted to no particular situation At times he obeyed simple

commands correctly but failed to accomplish any complicated acts. The inability to express himself was more than a dysarthria. He showed some degree of aphasia in addition to a profound intellectual deterioration.

Autopsy Report—In addition to the typical pathologic findings in the pyramidal tracts and anterior horn cells, the following changes were noted in the precentral areas and in the frontal convolutions, areas 8, 9, 10, and 11. The cortical layers of the frontal convolutions were narrower than normally. There was severe distortion in the arrangement of the cytoarchitecture with scantiness of ganglion cells. The nerve cells of the various layers were poor in Nissl substance. There were occasional neuronophagia and ischemic cellular changes. Small areas of destruction were found in the cortical layers. There was a slight increase in glial cells. There was an increase in the astrocytes in the adjacent white matter. The axis cylinders stained poorly and some were completely broken down. The changes in areas 4 and 6 were slightly less extensive (fig. 130). The second and third cortical layers on the left side were slightly damaged and contained an increase in glial cells. The giant pyramidal cells of Betz were diminished in number and showed many types of pathological changes.

Focal or Jacksonian Seizures

Jacksonian epileptic seizures as the result of a lesion or compression of area 4 are well known and accepted both on experimental and on clinico-
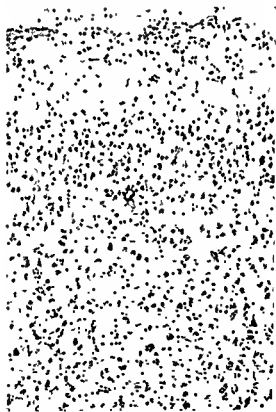
Fig. 130 (Case 6).—Slight distortion in the arrangement of the cytoarchitectural layers of area 6, with areas of devastation, dropping-out, and shadow-like appearance of nerve cells. Cresyl violet × 40.

pathologic grounds. Focal epileptic seizures, as originally described by Hughlings Jackson were reproduced experimentally by the application of electrical stimuli by remote control in the awake animal by a number of observers (Loucks, 1934; Chaffee and Light, 1934, 1935; and others). These seizures have a definite sequence and depend on the somatotopic organization of the motor area. Immediately after the seizure, the extremity may show signs of motor paresis (Todd's paralysis). There is sufficient evidence experimentally that the giant pyramidal cells of Betz of the fifth layer in area 4 are largely responsible for the production of focal or Jacksonian seizures. This has been shown in Fulton's laboratory where stimulation of the infant macaque did not result in focal seizures, due, presumably, to the fact that at this age the giant pyramidal cells of Betz are still undifferentiated. Shortly before myelinization adequate stimuli lead to focal seizures. Dusser de Barenne (1934b) was still able to obtain focal seizures when the first four layers were destroyed by laminar coagulation but not when the fifth layer containing the giant pyramidal cells of Betz was also involved. Furthermore, Marshall (1934) and Tower (1935) were unable to obtain focal seizures by stimulating area 4 after the medullary pyramids had been cut

CASE 7

P M, a woman, aged 46, experienced numerous Jacksonian seizures starting by twitchings of the muscles of the right side of the face and fingers of the right hand, spreading to the rest of the upper extremity and finally involving the lower extremity Shortly thereafter there was a transient weakness of the right upper and lower extremities On a few occasions these seizures were followed by a state of unconsciousness lasting two to three minutes

Neurological Examination—The findings included a slight motor weakness on the right side, slight hyperreflexia with Hoffmann and Babinski signs absent abdominals on the right side, and a slight nominal aphasia with a tendency to facetiousness The patient developed pneumonia and died before she could be operated upon

Autopsy Report—A tumor was present in the left hemisphere, involving areas 4 and 6 It extended from the Sylvian fissure to the superior surface of the hemisphere

This case could be duplicated with numerous others of neoplasms compressing or invading the premotor area.

Sphincter Disturbances

Bilateral lesions of areas 4 and 6 or their projection system may cause disturbances of urination and defecation. This is best seen in cerebrovascular diseases with multiple bilateral lesions. As these lesions are scattered, it is difficult to determine which part of the cortex is responsible for this disturbance in function. Sphincter disturbances are not observed commonly in amyotrophic lateral sclerosis, but I have observed a few cases of inability to control the vesical or rectal sphincters with this affection. In those cases of amyotrophic lateral sclerosis where such a disturbance was noted, areas

4 and 6 were involved. In the cases without cortical involvement there was no sphincter disturbance. In case 8, with bilateral compression of area 4, there was urinary incontinence (see Chapter XIV, p 393).

Forced Grasping and Groping

Forced grasping occurs in primates and man after lesions of the frontal or premotor areas. The first to call this to our attention, although his case did not come to autopsy, was Janischewsky (1909) who attributed this reflex to a lesion of the frontal lobe. Adie and Critchley (1927) were of the opinion that the presence of the grasp reflex with cerebral tumors is unequivocal evidence of the location of the tumor in the frontal lobe. This phenomenon is most outstanding when there are bilateral lesions of the premotor and possibly the motor areas. This reflex is affected by changes of position or posture.

The grasp reflex which appears after ablation of the premotor area in primates is apparently the result of removal of the inhibitory action of the cortical extrapyramidal pathways upon the subcortical centers As shown by Fulton and his co-workers (Bieber and Fulton, 1938) the grasp reflex becomes permanent only when areas 4 and 6 have been removed bilaterally.

Groping is also seen in monkeys from which the frontal and premotor areas have been removed bilaterally, or in humans with bilateral lesions of these regions. According to Fulton (1938) this reflex disappears when the pyramidal tract is destroyed and when vision is abolished. Groping is considered by most observers an automatic movement integrated at the cortical level.

The following clinicopathologic case of forced grasping and groping may throw some light on the site of the lesion.

CASE 8

G H , a woman, aged 50, noted slowly progressive weakness of the left side of the body Within a short period mental apathy, dullness, and facetiousness developed

Neurological Examination — Examination disclosed a left hemiparesis, Babinski's sign bilaterally, forced grasping and groping movements on the left, incontinence of urine, and bilateral papilledema

Autopsy Report — There was a huge neoplasm involving the right frontal and precentral regions, slightly encroaching on the left hemisphere and invading and compressing the corpus callosum (fig 131) The tumor did not invade area 4, but it compressed it and caused edema of its white matter The greatest part of the right side of the corpus callosum was destroyed by the tumor

There is no question that this tumor, although essentially situated on the right, also destroyed or compressed the left frontal and premotor areas, thus accounting for the grasping and groping reflexes Although the groping reflex disappears in the experimental animal when the pyramidal tract is

destroyed (Fulton, 1938; Bieber and Fulton, 1938), it was not abolished in this and other instances with compression or lesions of area 4 or of the pyramidal tract.

Another interesting fact in this case is the lesion in the corpus callosum and the presence of the grasp reflex. Richter and Hines (1934) and Kennard and Watts (1934) and others have observed that section of the

Fig 131 (Case 8) —Tumor of right frontal and premotor regions, slightly encroaching on the left hemisphere and invading and compressing the corpus callosum. Forced grasping and groping. Myelin sheath stain

corpus callosum does not in itself produce forced grasping. Kennard and Watts found that in a unilateral or bilateral premotor preparation from which forced grasping has disappeared, section of the corpus callosum did not cause the symptom to return. The corpus callosum in the present case did not play an important part in the inhibition of the grasp reflex. The grasp reflex in this and other instances became permanent, as in the experimental animal, because of the bilateral involvement of areas 4 and 6.

Posture and the Grasp Reflex—There is some experimental evidence that there is a relation between postural and grasp reflexes. Bieber and Fulton (1933, 1938) were of the opinion that the grasp reflex has become, in higher animals, a part of the righting reflex mechanism. Fulton and his co-workers observed that the grasp reflex in animals with bilateral ablations

of areas 4 and 6 is well marked only in the uppermost extremities when the animals are placed on their side. If the animal is lying on its right side the grasp reflex becomes more marked in the left hand. These observers have also noted that forced grasping following a unilateral lesion of area 6 is also responsive to change of position in space. Forced grasping cannot be elicited when the affected side is down, but it can be obtained when the involved extremity is uppermost. Viets (1934), Kennard, Viets, and Fulton (1934), and others have observed changes in the intensity of the forced grasping with changes in position in human cases. The following clinico-pathologic case illustrates this.

Fic 132 (Case 9) —Tumor involving left premotor convolutions, including areas 4 and 6 and part of the temporal convolutions Destruction of part of the fibers of the corpus callosum Forced grasping and groping Myelin sheath stain

CASE 9

H I, a man, aged 28, had a fainting attack and loss of consciousness followed by severe headache, non-projectile vomiting lassitude, and weakness of the right side of the body

Neurological Examination—On the right side, the following were disclosed motor weakness, slight spasticity, increased tendon reflexes, Babinski's sign, and forced grasping When lying on his right side the grasp reflex was very weak or could not be elicited at all When lying on his left side the grasp reflex became very marked The right side of the body in this instance was warmer than the left and was slightly edematous

Course—A left frontal craniotomy was performed with partial removal of a tumor from the frontal region and area 6, followed by a marked right hemiplegia, aphasia, a meningitis, and disappearance of the grasp reflex

Autopsy Report—A large tumor involved the left frontal convolutions, including part of areas 4 and 6 and part of the temporal convolutions (fig 132) Some of the fibers of the corpus callosum on the left side were destroyed or stained very poorly

This case not only confirms the findings of Kennard, Viets, and Fulton (1934) on the relation of the grasp reflex to posture, but also illustrates the relation of vasomotor changes, as evidenced by the edema and increase in warmth of the right side of the body, to precentral lesions.

That the grasp reflex is part of the postural mechanism has been shown by Fulton and Dow (1938) on labyrinthectomized monkeys. On bilateral removal of areas 4 and 6 from a bilaterally labyrinthectomized macaque, the grasp reflex became modified by the rotation of the head. With the animal in a supine posture the grasp reflex was completely inhibited on the side towards which the chin was rotated, and increased on the opposite side. This is in harmony with the Magnus-de-Kleijn phenomenon in which rotation of the head arouses extension of the extremities on the chin side and flexion on the opposite side. The grasp reflex thus is part of the postural reflex mechanism and is affected by the tonic neck reflexes.

A number of cases of lesions of the precentral region extending also into the parietal and temporal areas were observed by the author in which there was a relation between the grasp reflex and posture. The following case, which came to necropsy and has been previously reported by Wechsler, Bieber, and Balser (1936), illustrates this point.

CASE 10

S. G., a woman, aged 49, was semistuporous and had a right hemiplegia, right hemisensory disturbances, hemianopsia, and aphasia. Several hours before death, decerebrate rigidity and forced grasping bilaterally were noted. When the patient was placed in the lateral position, the grasp reflex became accentuated on the uppermost side and diminished on the lowermost side. If the patient was turned to the opposite side the activity was reversed, the grasp reflex was again accentuated on the uppermost side and depressed on the undermost side. The reflexes were approximately equal when the patient was on her back.

Autopsy Report—A large glioblastoma multiforme was present in the left frontal, premotor, motor, temporal, and parietal areas.

The grasp reflex in this instance was most likely caused by involvement of areas 4 and 6, and apparently remained unchanged by the extension of the neoplasm to other regions.

Lesions Outside the Precentral Region—This brings up the question whether the grasp reflex is totally the result of lesions of the frontal cortex and of areas 4 and 6. I have observed a number of cases of grasp reflexes with tumors or lesions of the temporal or parietal lobes or in the posterior fossa without involvement or invasion of the areas 4 and 6. Frazier also noted forced grasping in instances where areas 4 and 6 were spared. In most of these cases, however, compressions of areas 4 and 6 could not be totally excluded.

Bucy (1931) found bilateral reflex grasping in two cases of tumors not situated in the frontal lobe. In one the tumor was situated in the fourth ventricle; in the other, in the right occipital lobe. In both instances, however, there was a marked internal hydrocephalus. Similar observations were also previously reported by Janischewsky (1928) and Fedorovoa (1929). As a result of these findings, Bucy was of the opinion that bilateral reflex grasping in the presence of a marked internal hydrocephalus or increased intracranial pressure is of questionable value as a localizing sign. Freeman and Crosby (1929) also pointed out that bilateral reflex grasping is not of as much value as a localizing sign as when this sign exists on one side alone.

The following case of forced grasping with a lesion in the posterior fossa shows that this reflex may occur with lesions other than in the premotor region. It is similar in many respects to Bucy's case of forced grasping with a tumor in the fourth ventricle.

CASE 11

A A, a woman, aged 33, developed severe morning headaches associated with vomiting, dizziness, diminution in vision, yawning, and hiccoughing

Neurological Examination—The patient had a marked memory defect, unsteady gait, a tendency to fall backward, and other cerebellar signs, bilateral grasping and groping and a tendency toward exaggeration of the tendon reflexes which was greater on the right side but without pathological reflexes There was marked papilledema, nystagmus in all directions, and deviation of the jaw and palate to the left

Autopsy Report—There was a tumor in the fourth ventricle and a marked internal hydrocephalus

Autonomic Disturbances

Autonomic disturbances following lesions in areas 4 and 6 are rare. Vasomotor phenomena such as increases in temperature on one side of the body, changes in the pulse, respiration, blood pressure, discoloration of an extremity, edema, and increase in sweating, I have observed in cases with parietal lobe lesions. In Case 9, where a tumor in the left posterior frontal region was associated with forced grasping and groping, the right side of the body was slightly edematous and was warmer than the left. Experimentally, transient increases of temperature of a monoplegic extremity were observed by Pinkston, Bard, and Rioch (1934) in a chimpanzee following an isolated removal of area 4 Hoff and Green (1936, 1937) obtained elevation of blood pressure and shift of the blood from the visceral into the muscular bed following stimulation of area 4 of the macaque. More pronounced vasomotor effects were obtained following lesions of area 6 or of a combination of areas 4 and 6. Aring (1935) observed that animals with lesions of area 4 developed symmetrical shivering when exposed to a reduced temperature, long before there was any drop in the rectal temperature (see Chapter XI).

The Precentral Cortex and the Extrapyramidal System

The precentral cortex in higher forms gives rise to extrapyramidal pathways which end in many of the extrapyramidal nuclear masses. Mellus (1895) firmly believed that area 4 contributes extensively to the extrapyramidal projection system. Levin (1936) showed that in the macaque the extrapyramidal projections from areas 4 and 6 are indistinguishable on the basis of their distribution and destination; they each contribute projections to the pons, substantia nigra, mesencephalic tegmentum, and red nucleus (see Chapter V).

It seems justifiable to analyze a number of classical clinicopathologic cases with involuntary movements which showed, in addition to lesions in the basal ganglia, lesions of area 6 or other cortical extrapyramidal areas. It should be emphasized, at the outset, that the involuntary movements most likely develop because of the lesions in the basal ganglia rather than as a result of the much less constant and more variable cortical lesions.
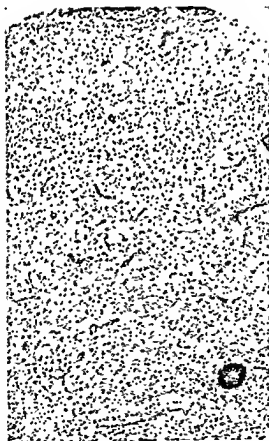
FIG. 133 (Case 12) —Post-encephalitic paralysis agitans with involvement of area 6. Notice distortion in the arrangement of the cytoarchitectural layers and diffuse perivascular infiltrations. Cresyl violet x 40

These cases, however, are significant, for they illustrate that in extra-pyramidal disorders the lesions are not strictly limited to the basal ganglia.

A number of extrapyramidal diseases were studied. These included paralysis agitans, chorea, dystonia, hepatolenticular degeneration, etc.

Paralysis Agitans—Thirty-seven cases of paralysis agitans studied and previously reported (Davison) were divided into three groups: (1) post-encephalitic paralysis agitans (12 cases); (2) idiopathic paralysis agitans (7 cases); and (3) atherosclerotic paralysis agitans (18 cases).

Post-encephalitic Paralysis Agitans. Pathological or significant changes in areas 4, 6 and 8 in this group were noted only in two cases. In these, there were inflammatory changes, perivascular infiltrations and distortion of the cytoarchitecture of areas 4, 6 and 8 (fig. 133). One case will be described to illustrate the pertinent facts.

CASE 12

H. S., a man, aged 53, developed influenza in 1918. About sixteen years later he developed tremor and rigidity.

Neurological Examination—The neurological examination disclosed a parkinsonian facies and attitude, generalized muscular rigidity, lack of associated movements, and marked pill-rolling tremor and tremor of the distal parts of the upper extremities. The tremor could be stopped momentarily by voluntary action. The speech was slow and monotonous. There were also rhythmic "champing" coordinated movements of the lower jaw, lips, chewing-like movements, salivation, and oculogyric crises.

Autopsy Report—In addition to the typical findings in the globus pallidus and substantia nigra, there were also pathologic changes in areas 4, 6, and 8. There were perivascular infiltrations, distortion of the cytoarchitecture (fig. 133), and a few foci of cellular devastation. The nerve cells throughout these areas stained poorly, some showed neuronophagia, satellitosis, ischemia, and severe cell changes of Nissl. There was an increase in glial nuclei.

The rhythmic, "champing," coordinated movements of the jaws and lips, the chewing-like movements and salivation are not unlike the phenomena observed in monkeys upon stimulation of area 44. Foerster on stimulating this area (his area 6b) in man obtained continued movements, rhythmic and coordinated in character, of the lips, tongue, mandible, pharynx, and larynx. Some of these consisted of chewing, licking, salivation, swallowing, mastication, croaking, and grunting. The oculogyric crises in this patient may have been caused by impulses from area 8. Conjugate movements and other ocular manifestations have been obtained by stimulating this area in monkeys and man (Grunbaum and Sherrington, 1901; Bender and Fulton, 1938; Foerster, 1936b; and Penfield and Boldrey, 1937).[4]

[As Dr. Davison stated earlier, the involuntary movements develop as the result of lesions in the basal ganglia and not from lesions in the cerebral cortex. That is well illustrated by the cases mentioned here, for whereas such movements as these are common with post-encephalitic parkinsonism Dr. Davison found cortical lesions in only two out of twelve cases. Furthermore, as Dr. Davison points out, the movements are similar to those produced by cortical stimulation, thus indicating that in disease these movements appear because of released cortical activity. (See Chapter XV.)—Editors.]

Idiopathic Parkinsonism. Eight cases were present in this group. None of these had "champing" movements, and ocular manifestations were present in only two cases. In one there was slight difficulty in convergence, in the other bilateral ptosis. Areas 4, 6, and 8 and other cortical areas in this group showed no pathologic changes.

Of interest was the effect of a chordotomy on the tremor and rigidity in one case of this group. Following sectioning of the crossed pyramidal, rubrospinal, spinothalamic and spinocerebellar pathways, the tremor and rigidity disappeared. The influence of the pyramidal tract on such symptoms will be discussed in detail under atherosclerotic parkinsonism.

Atherosclerotic Parkinsonism. Eighteen cases belonged to this group. All of these showed some clinical and pathological evidences of atherosclerosis of the central nervous system. Ocular manifestations were not present in any of the cases, except for a rotary nystagmus in two instances. Clinical evidence of damage to the pyramidal tract was present in seven cases. In one the tremor disappeared on the left side and the rigidity became less marked following thrombosis of the right lenticulo-striate artery. In the six other cases there was no cessation or lessening in the tremor and rigidity despite such involvement.

Microscopically areas 4, 6, and 8 and other cortical regions showed significant changes in thirteen instances in this group, in contrast to the cases of post-encephalitic and idiopathic parkinsonism. The picture was varied and consisted of a slight distortion in the arrangement of the cyto-architectural layers, small areas of devastation, dropping-out of nerve cells, pallor of nerve cells, chronic and ischemic cell changes, perivascular edema, atherosclerotic changes in the small cortical vessels and proliferating vessels. In three cases there were small areas of softening Subsequent to my investigation, Benda and Cobb (1942) studied eight cases of paralysis agitans that came to necropsy. In contrast to the cases I reported they found in all their cases changes in the frontal areas and in area 6, while area 4 was intact in all instances.

The changes in areas 4, 6, and 8 in my cases were undoubtedly secondary to the generalized atherosclerosis. Whether the association of these cortical lesions with those in the pallidum and substantia nigra had any influence on the production of tremor and rigidity is difficult to state. The presence of tremor and rigidity in most of the post-encephalitic and in all of the idiopathic groups without such cortical involvement, would seem to rule out such a possibility.

The influence of the intactness of the pyramidal tract or of area 4 on the involuntary disturbances and rigidity will be illustrated by one case from this group.

CASE 13

W. E., a woman, 65 years of age, gave a history of a pill-rolling tremor which began in the right hand and then spread to the left hand. She also suffered from hypertension and a generalized atherosclerosis.

Neurological Examination—On admission the patient showed the typical manifestations of paralysis agitans with parkinsonian facies, pill-rolling tremor and tremor of the jaw and extremities, rigidity, cogwheel phenomenon, and lack of associated movements. About ten months after admission there developed a hemiplegia on the left side of the body. At this time the tremor disappeared in the left extremity while the rigidity and cogwheel phenomenon were lessened on that side. The deep reflexes were exaggerated on the left and were associated with Babinski and allied signs.

Autopsy Report—*Cortex* Sections through various regions of the cortex, including areas 4, 6, and 8, disclosed moderate atherosclerosis of the small cortical vessels and slight thinning of the gray matter, especially on the right side, but without significant distortion of the cytoarchitecture.

Basal Ganglia The greatest part of the right caudate nucleus, putamen, globus pallidus, external capsule, claustrum, and internal capsule were destroyed and showed changes usually seen with occlusion of the lenticulo-striate artery (fig 134) The left caudate nucleus and putamen were normal The left globus pallidus, however, was slightly shrunken, stained poorly and had a slight lacunar appearance (fig 134) The left anterolenticulars was slightly thinned The left pulvinar and the substantia nigra showed the typical changes seen in parkinsonism Sections through the medulla oblongata and spinal cord revealed a descending demyelinization of the right pyramidal pathways

Fig 134 (Case 13)—Atherosclerotic parkinsonism with abolition of tremor and rigidity on the left following thrombosis of right lenticulo-striate artery Notice the marked destruction on the right of the striatum, pallidum, and internal capsule The changes in the left pallidal segments are typical of those found in parkinsonism Myelin sheath stain

In this case the tremor on the left side disappeared and the rigidity and cogwheel phenomenon lessened following thrombosis of the right lenticulo-striate artery with destruction of the right pyramidal tract. A

similar change was noted above in a case of idiopathic parkinsonism following a lateral chordotomy These cases seem to indicate that the tremor is mediated via the pyramidal pathways

Bucy and Case (1937) abolished unilateral tremor in one instance by excision of areas 4 and 6. Klemme (1940a) is said to have alleviated tremor by extirpating the premotor cortical areas in a large number of cases of paralysis agitans, but the descriptions of his surgical procedure are not sufficient to permit of any evaluation of his cases. Putnam obtained relief of tremor in two cases after removal of part of the precentral gyrus and in three other cases (1940a). the tremor disappeared largely or entirely after section of the lateral pyramidal tract in the spinal cord. Aring and Fulton (1936) abolished intention tremor in the monkey by removal of the precentral cortex (areas 4 and 6) In connection with the abolition of tremor following pyramidal tract lesions Parkinson, as early as 1817. observed that the tremor disappeared following a hemiplegia and recurred as the paralysis became less marked. He also mentioned that voluntary effort may, for a short time. also stop the tremor and reduce the rigidity in some instances, while in others voluntary effort may increase both. Since voluntary effort is transmitted through the pyramidal tract, this pathway shows "almost an ambivalent function in regard to tremor" (Putnam). The tremor in some of the parkinsonians. especially the atherosclerotic cases (Davison). did not disappear despite the apparent involvement of the pyramidal tract as evidenced by hyperreflexia and Babinski sign. Benda and Cobb (1942). on the basis of their investigations and that of Klaue (1940). mention that. in Parkinson's disease, atherosclerotic alterations of the cortex are almost absent and that the tremor of paralysis agitans can only occur when the motor cortex is largely intact.

In the eighteen cases of atherosclerotic parkinsonism Davison reported. area 4 was found involved in various degrees in thirteen cases. Fulton pointed out that. if area 4 is removed. tremor may still occur. Some familial cases of pallido-pyramidal degeneration which I have observed are further evidence that tremor and rigidity may coexist with lesions of the pyramidal tract. These patients have rigidity. tremor. parkinsonian facies and a bilateral hyperreflexia with pathological reflexes From these cases it cannot be definitely concluded that tremor is present only when the pyramidal tract is intact or that the impulses producing tremor are conducted only along the fibers from areas 4 and 6.[5] Of further interest are the experimental results of Browder and Meyers in man with parkinsonism. At first

[5] [It should be noted here that hyperreflexia and spasticity are evidence of involvement of the extrapyramidal or parapyramidal fibers from the precentral cortex and not evidence of involvement of the pyramidal tract. Furthermore. partial injury to area 4 or to the pyramidal tract are not comparable to ablation of area 4 or complete interruption of the tract —Editor.]

these authors interrupted the "U" fibers between areas 4 and 6 without any appreciable changes in the tremor. They then undercut area 6 without any effect. By extirpating, however, partially or totally, the caudate nucleus, there was an "enduring" cessation of the tremor in some cases Apparently other structures beside the caudate nucleus must have been injured in these operations. Putnam's contention that the cortical incision which Meyers made and the operative procedure are enough to injure the projection fibers from the cortex, especially from areas 4 and 6, and thus produce the same physiologic effect as is obtained with the older procedures, seems justified (see Chapter XV).

Although there are numerous discrepancies, one may assume that areas 4 and 6 and their projection systems are the neural mechanisms through which involuntary movements are transmitted.

Other Extrapyramidal Disturbances—Chorea. The involuntary movements seen in chorea, dystonia, hepatolenticular disease, myoclonus epilepsy, and spastic pseudosclerosis likewise cannot solely be explained by disturbed function of the striatum and globus pallidus Wilson (1929) believed that, for the appearance of these involuntary movements, the corticospinal tract must remain intact. He concluded that chorea and choreo-athetosis represent a complex type of involuntary movements for the production of which a motor mechanism having its seat in the cortex is required. On this basis, Horsley excised a part of the motor area to relieve a case of hemichorea Bucy, in a case of left choreo-athetosis, removed most of the representation of the left upper extremity in area 6, leaving the posterior part of the precentral gyrus (the area gigantopyramidalis) largely intact. Following this procedure, the choreo-athetosis temporarily disappeared and was permanently diminished. Subsequently Bucy excised areas 4 and 6 in a few other cases and the choreo-athetoid movements disappeared. Sachs obtained similar results. From these and other cases, it may be stated that areas 4 and 6 are largely responsible for the involuntary movements observed in these extrapyramidal disorders (see Chapter XV).

Areas 4, 6, and 8 and other cortical regions were found involved in a number of cases of chronic progressive chorea (Davison, Goodhart, and Shhonsky, 1932) and further unpublished cases of variable etiology (Davison). It will not be necessary to further illustrate chorea by case histories; the reader is referred to Case 5, described earlier in this chapter. The cortical changes observed in these cases raise the question of the relationship of destructive lesions in this precentral region to the release of involuntary movements.

Dystonia Musculorum Deformans. The same may be said about dystonia musculorum deformans where changes in the precentral motor cortex

were described by Davison and Goodhart (1938) and others. The following case, in which excision of the right premotor cortex was performed, illustrates this.

CASE 14

M. S., a girl, aged 12, developed whooping cough at the age of 6 weeks After the first paroxysmal attack of respiratory dyspnea and cyanosis, the mother noticed that the

cular tonus alternated between hypotonia and hypertonia The deep reflexes could not be elicited on the right because of the marked muscle spasm, there were no patho-
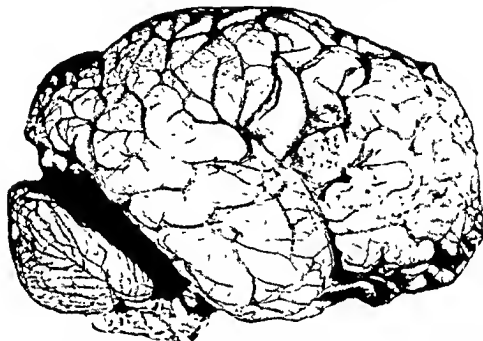
Fig 135 (Case 14)—Notice post-operative scar in the right premotor area Lateral view The dystonic movements on the left side were not lessened [It is noteworthy that the lesion is in the inferior part of the frontal lobe near the face field approximately in areas 44 or 45—cf fig 2, p 11—rather than at the level of the arm and leg fields —Editor]

child had a vacant stare and the right upper extremity was held in posterolateral extension and rotated inward with the palm upward She recovered completely and remained well until the age of 2½ From then on dystonia, athetoid and massive swinging movements of the right upper limb set in

Neurological Examination—There were marked dystonic movements of practically all muscle groups, slight facial grimacing when at rest, and athetoid movements of the fingers and toes The dystonic movements increased on voluntary effort. Mus-

logical reflexes The patient was dysarthric but not aphasic Spasmodic torticollis and hypertrophy of the left sternocleidomastoid muscles were present

Course—Excision of the right premotor cortex was performed for relief from the dystonic movements The patient's condition remained unchanged after operation[*]

Autopsy Report—Cortex There was a post-operative scar at the site of excision of the right premotor region (fig 135) There was shrinkage of the basal ganglia Microscopic examination of the right premotor

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[*] [As fig 135 clearly shows, the extirpation lies just above the Sylvian fissure, much further ventralward than the effective extirpations of Bucy and of Putnam and considerably below the "arm" area —Editor]

area (area 6) disclosed distortion of the cytoarchitecture Many of the layers were destroyed and replaced by glial tissue and proliferated vessels The remaining nerve cells showed many types of pathological changes. The left precentral and other cortical areas showed thinning, a slight distortion in the arrangement of the cyto-

architecture, with small areas of devastation (fig 136) and many types of pathological changes in the ganglion cells The pathological process was most pronounced in the frontal and precentral regions The pathology of the basal ganglia is omitted from this presentation The reader can refer to the original article (Davison and Goodhart, 1938)
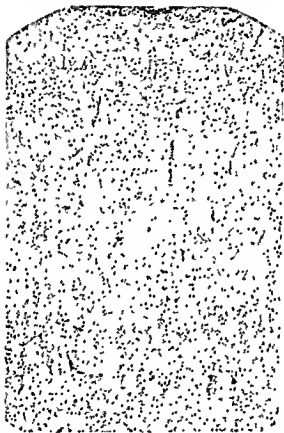
FIG 136 (Case 14) —Left area 6 from a case of dystonia musculorum deformans Notice distortion in the arrangement of the cytoarchitectural layers, dropping-out of nerve cells, and areas of devastation Cresyl violet x 40

The above and other cases with disease of area 6 as well as the case of Munch-Peterson (1935), who reported dystonia in a patient with a diffuse inflammatory process in the cerebral cortex, especially in the frontal lobes, without abnormalities of the basal ganglia, suggest the relationship of these areas of the cortex to the "extrapyramidal" diseases. Of interest is the lack of amelioration of the dyskinesia when this part of the right precentral region was excised in the above case.

Similar changes in area 6 were observed in a series of cases of spastic pseudosclerosis (Davison, 1932, and Davison and Rabiner, 1940), myoclonus epilepsy (Davison and Keschner, 1940), and a number of unpublished cases of progressive hepatolenticular degeneration. Only one case in the latter group will be described.

CASE 15
Progressive Hepatolenticular Degeneration

G. J., a man, aged 34, had an upper respiratory infection at 17, following which there appeared diplopia, progressive rhythmical shaking movements of the fingers of both hands, and difficulty in speech.

Neurological Examination—There was coarse oscillatory tremor of the entire body, most marked in the extremities, with rhythmical nodding of the head. The tremor of the upper extremities was typical of the "Flügelschlagen" seen in this disorder. There was marked rigidity with cogwheel phenomenon in all extremities, most marked in the upper extremities. There was a mask-like facies with gaping of the mouth and oscillatory movements of the jaw. At the corneoscleral junction there was a brownish discoloration and the pupils reacted sluggishly to light.
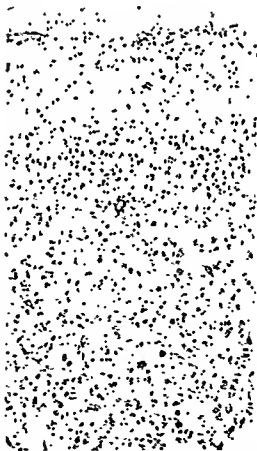
Fig. 137 (Case 15)—Section from the precentral region from a case of hepatolenticular degeneration showing distortion in the arrangement of cytoarchitectural layers and dropping out of nerve cells. Most of the changes are seen in the lowest three layers. Cresyl violet × 30.

Autopsy Report—General Organs There was a typical atrophic cirrhosis of the liver and splenomegaly as seen in hepatolenticular degeneration.

Cortex. Sections of the precentral motor cortex disclosed a distortion of the cyto-architecture. The giant pyramidal cells of Betz, although present, showed marked loss of Nissl substance, and some had a shadow-like appearance. The lowest three layers in these regions showed most of the pathologic changes (fig 137); they also contained numerous Alzheimer glial cells, Type II. In sections through area 8 there was a marked distortion of the lowest three cortical layers, and an increase in microglial cells and Alzheimer glial cells, Type II. The nerve cells stained poorly and some showed various types of pathological changes. Areas of devastation in the vicinity of the perivascular spaces were outstanding. The section through the basal ganglia disclosed a typical pathological picture as seen in Wilson's disease.

Disturbances in Ocular Movements

The Motor Eye Field (Area 8)—Only disturbances in ocular movements which are linked with lesions in area 8 will be discussed. The frontal eye field (area 8), first accurately demonstrated by Beevor and Horsley (1890b) and by Grünbaum and Sherrington (1901), occupies a small area of the cortex in man and forms the posterior part of the second frontal convolution. Grünbaum and Sherrington (1901), Leyton and Sherrington (1917), Bender and Fulton (1938), Foerster (1936b), and others showed that faradic stimulation causes conjugate movements of the eyes to the opposite side and opening of the eyelids (see Chapter XII). Epileptiform attacks have also been induced in man by stimulation of this area, the seizure beginning with clonic lateral movements of the eyeballs.

The following case of myoclonus epilepsy with myoclonic movements in the eye muscle is of interest in this connection. Although these myoclonic movements were generalized, and although most of the pathologic changes were present in the basal ganglia, the possible relationship of the ocular disturbances to the changes found in area 8 are interesting to contemplate (see Davison and Keschner, 1940).

CASE 16
Myoclonus Epilepsy

V D, a woman, aged 23, complained of jerky movements of the body and generalized convulsions with loss of consciousness. The jerky movements of the body, face, and eyes were spasmodic and lightning-like in rapidity. During some attacks the eyelids closed and trembled, during others, they were open and the head turned to the right.

Neurological Examination—The essential neurologic findings were eccentrically situated pupils, reacting sluggishly to light; myoclonic movements of the muscles of the eyes, face, tongue, and extremities. The eyes closed and opened during these attacks and would turn in conjunction with the head to the right. There were also bradykinesia, diminished associated movements of the arm in walking, slight rigidity with a cogwheel phenomenon in mild extrapyramidal attitude, monotonous dysarthric speech, and clumsiness in performing skilled acts. The patient was dull, retarded, and unresponsive mentally.

Autopsy Report—Cortex. The frontal convolutions, areas 4, 6, and 8 showed the following. There was a slight distortion of

the cytoarchitecture with occasional dropping-out and pallor of the nerve cells and prominence of the nuclei Inclusion bodies were present in the ganglion and glial cells Many of the nerve cells with inclusion bodies were deformed and showed various pathological changes Small areas of devastation were also noted Similar and extensive changes were found in the substantia nigra

Although the pathologic process was widespread, it is possible that the release of generalized clonic movements and other extrapyramidal symptoms was influenced by the lesions in areas 4 and 6. The ocular manifestations, such as the conjugate movements, the opening and the closing of the eyelids and turning of the head may have been related to the lesions in area 8. The mental picture was probably caused by the lesions found in the frontal and other convolutions.

Summary

In spite of the occasional apparently contradictory clinical findings cited, it is obvious that the precentral motor cortex is closely related to the postural and righting reflexes; and that whereas destruction of areas 4 and 6 usually results in spasticity and hyperreflexia, lesions of area 4 alone are commonly associated with flaccidity. Involvement of the postcentral region with resulting sensory disturbances may also be associated with flaccidity. The exact interpretation of this fact awaits further study.

Destructive lesions of the precentral motor cortex, especially of area 4, result in the impairment of volitional and skilled movements. The defect is greatest in the highly organized and finely coordinated skilled movements of the digits. Bilateral lesions of the precentral motor cortex result in disturbances of the sphincters. On the other hand, irritative lesions of the precentral motor cortex cause focal or Jacksonian convulsive seizures.

Forced grasping and groping usually are associated with lesions in the posterior part of the upper frontal convolutions, with involvement of areas 4 and 6. The grasp reflex, in view of its occasional occurrence in association with lesions in other parts of the brain, becomes of questionable value as a localizing sign in the presence of marked internal hydrocephalus or severely increased intracranial pressure.

Autonomic disturbances may occur in association with lesions in the precentral motor cortex.

Temporary paralysis of conjugate lateral movement of the eyes toward the opposite side frequently results from destructive lesions in area 8, whereas irritative lesions of areas 6 and 8 cause involuntary turning of the head and eyes toward the opposite side.

When lesions of the precentral motor cortex are associated with involvement of the frontal areas lying farther forward, i.e., areas 9, 10, 11, 12, etc., behavior disturbances may occur.

Chapter XVIII

SIGNIFICANCE OF THE PRECENTRAL MOTOR CORTEX

Marion Hines, Ph.D., Sc.D.

Professor of Experimental Anatomy
and Research Assistant in
Physical Medicine
Emory University
Atlanta

OUTLINE OF CHAPTER XVIII

Significance

SIGNIFICANCE OF THE PRECENTRAL
MOTOR CORTEX

METHODS AND TERMINOLOGY

THE DETERMINATION OF SIGNIFICANCE is a cortical act, and requires the integrity of large areas of the cortical surface together with subcortical and intracortical connections. The word significance requires two modifying phrases expressing relation, one of possession, naming the object, and the other of purpose, outlining the limits to which the first phrase may be applied. The significance of any part of the central nervous system must be gauged by a just and logical appraisal of the results of methods used to study its contribution to the activity of the whole intact organism. Two methods are in general use: (1) comparison of the normal activity under investigation with change observed subsequent to removal or injury of the particular region, and (2) the recording of stimulation of that area, either directly by the electric current or indirectly by the stimulation of nerve paths which impinge upon it. The first method is indirect, for the results of ablation are, indeed, only the sum of the total activity of the remaining tissue. The second method is more direct but at best grossly artificial. Because the human "mind" demands that the results of methods used to study a part of a phenomenon fit into a logical scheme, the results obtained by each of these methods must be at least partial reciprocals of each other. In the case of the "motor" cortex of the frontal lobe, these methods have indicated that its contribution to function is limited to the control of the effector systems of the animal body. This particular tissue is therefore unconcerned with the activity of the special senses or with the "higher" integrative function of the cortex cerebri. It is, in Hughlings Jackson's terminology, the middle level. A third method of study may be applied to the elucidation of the contribution of this middle level to function; for changes in motor performance which accompany growth of individual animals of a single species should logically recapitulate in some ways the results of ablations of parts of the precentral motor cortex.

This introduction implies that the "motor" cortex can be identified and delimited. Its limits will be dependent upon its definition. And its definition can be established either by a distinctive structure or a peculiar function. The distinctive structure of the precentral motor cortex could depend upon its cytoarchitecture, or upon the peculiarity of either its afferent or efferent connections; or, conceivably upon characteristic intracortical relations. Or, again, it is possible that, having discovered an element of struc-

ture which delimited it accurately, no corresponding characteristic function could be demonstrated.

Besides these difficulties, inherent in our present approach to the interpretation of that which the "motor" cortex contributes to the animal's use of its effector mechanisms, there are others. These have their origin in the necessity of using terms of description for the assay of results either of ablation or of stimulation of this region. The majority of these terms of description fall into three general classes: (1) those which are patently erroneous, (2) those which are loosely used, and (3) those which start a train of implications. Frequently the movements made by a primate subsequent to ablation of the precentral gyrus are described as involuntary, allocating to the function abolished the adjective voluntary. And yet a primate which has suffered such a loss is able to take food with the hand opposite the lesion. Was that movement involuntary? Certainly, it looked as if he was able to accomplish the desired end.

The use of muscles opposite the lesions changes with time. This change for the better if it is great has been described as restitution when only improvement is meant. There is always a residual loss, if the operation has removed the whole of the precentral gyrus which controls the extremity in question. In too many descriptions of the state of skeletal muscle subsequent to surgical removal of this area, such adjectives as defective or weak have replaced accurate descriptions of how the individual uses the muscles opposite the lesion.[1] What, for example, does the sentence, "All movements of the fingers were defective," mean? Could they be flexed, extended, abducted or adducted partially or were some of these movements better accomplished than others? Was it necessary for the patient to fix proximal muscles to accomplish one or all of these muscular contractions? How much effort did the contractions which could be accomplished take? What does "a weak contraction" mean? That only a part of the muscle fibers within the muscle contracted or that the rhythm of contraction was altered? Again was this weakness of contraction accompanied or unaccompanied by movement in cooperating muscles? How did the antagonists behave?

Apparently the adjective exaggerated as applied to tendon reflexes is used in two ways: (1) to describe a greater than normal arc of movement, and (2) to express the shortened latent period of the spastic tendon jerk.

The use of the term "upper motor neuron lesion," as a contrast to

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[1] Hemiplegia and its allied disorders of movement do not have that quality of newness which stimulates accurate description. A comparison of recent clinical textbooks in Neurology with those written 50 years ago will demonstrate to the doubtful that the authors of the latter were writing what they had seen the patient do. Only when the results of injury to the central nervous system can be expressed in mathematical formulae can Hughlings Jackson's advice be disregarded

"lower motor neuron lesion," has caused many to attribute the sequelae of damage to the cerebral motor systems to injury of a single corticifugal system, the pyramidal tract. Such thinking denies participation in the results of such lesions to other known corticifugal systems. For years the paralysis and the spasticity resulting from injury to the internal capsule or to the cortical surface of the precentral gyrus have been explained by the loss of this single corticifugal system. On the one hand that system prevented the appearance of Jackson's phenomena of release, and on the other produced voluntary movements! In turn the prevention of the appearance of the former group of sequelae came to be explained by the term inhibition.[2] It may be too much to ask that the use of explanatory terms be postponed until the explanation is forthcoming and that descriptive terms be substituted. The hierarchy of levels as used in the central nervous system implies that each in turn "inhibits" the uncontrolled activity of those below it. Such a concept serves a real purpose if it is recognized that it is only a concept of action within the central nervous system, neither an explanation nor a cause. But the thinking of man slips so easily!

Although there is a growing comprehension that in general "centers"[3] in the central nervous system are incapable of isolated function, nevertheless the urge to allocate function in structure remains. This urge seems to be a fundamental part of human thinking, for having discovered a morphologically discrete area a distinctive contribution to organized activity is sought. And the cerebral mantle is no exception. Further, the compulsion to place function in cortical space has been productive, as a comparison of the results of cortical removals in animals without regard to cortical structure (see Hines, 1929) with those which have been made since that date with an eye on structure is witness. The constraint to relate structure and function is sound, but it must be done with understanding of inherent limitations.

This appraisal of the contribution made to the control of movement by the precentral motor cortex will be attempted with as little use of customary terminology as possible.

[2] The writer of this chapter is in thorough agreement with Benda and Cobb (1942) about the use of this word. Although the original meaning of the word is "to hold in check," it is now used for the most part as if it meant "to stop" (see the Oxford Dictionary). In the case of a relaxation of tonic innervation of skeletal muscle elicited by electrical stimulation of the surface of the cortex cerebri Hines and Boynton (1940) used the term chalasis. That word expresses what is seen and has no implications. Perhaps the time is almost ripe to reassess the action of the "higher" levels of the central nervous system upon the "lower" levels in such a way that the production of relaxation by them is distinguished from the suppression which they exert and from their more elaborate activity of control.

[3] Reviewing the history of the use of the term "center" for any particular region within the central nervous system suggests that it is used during the earlier stages of development of knowledge of function of the region under scrutiny.

ARCHITECTURE

The precentral motor cortex includes the whole of Brodmann's areas 4, 6, and 44, the area frontalis agranularis and dysgranularis. It is von Bonin's precentral subsector, the recipient of thalamocortical fibers from the anterior division of the ventrolateral nucleus of the thalamus, which in turn is the terminus for the dentatothalamic tract. These thalamocortical fibers terminate apparently without discrimination throughout the whole precentral subsector in the axonal plexus of the lower part of layer IIIc and the just visible layer IV.

The association or commissural fibers connecting the homologous heterolateral areas of the whole precentral subsector are similar. Each of the subdivisions of the precentral subsector are similarly related, (1) with the contralateral areas 4 and 6 and (2) with areas 1, 5, and 7 of the parietal lobe. The whole precentral subsector receives homolateral association fibers from areas 1, 2, 3, and 5 of the parietal lobe, and from 21 and 22 of the temporal lobe.[4] Area 4 receives terminals originating in area 7 of the parietal lobe, and in areas 8, 9, and 10 of the frontal lobe. The upper part of area 6 receives fibers from area 4; lower 6, from area 10. It is very peculiar that no short association fibers have been described connecting areas 8 and 6, and that none have been found which originate in 6 and terminate in 4. These connections have been determined by microscopical studies, largely with the Marchi method. It should be noted that the results of this method are not always in agreement with the results of the electrical methods (neuronography) as reported by McCulloch in Chapter VIII.

Both the homolateral and heterolateral association axons terminate in layers II and IIIa and in layers Vc and VI. Cajal believed that the cell bodies of fibers passing through the corpus callosum were pyramidal cells in layers II and IIIa, and Fines (cited by von Economo and Koskinas, 1925, p. 183) that these fibers arose from cells in layer V.

The corticofugal fibers from the precentral subsector are axons of pyramidal cells in layer Vb. To this origin Cajal would add the spindle cells of layer VI and the pyramidal cells of layer IIIc. Assignment of these cells as origins for definite tracts is not possible at the present time.[5] Retro-

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[4] The careful reader will note that the writer has left out area 17, which Walker included (Chapter IV). This was done because Le Gros Clark's (1941) careful work on the area striata lead him to believe that if the lesion was small and confined to area 17, no association fibers extended further than 5 mm. This interpretation of degeneration is at variance with that of Mettler (1935), as Walker showed.

[5] Von Economo and Koskinas (1925) may be consulted (p. 181) by anyone who is curious enough to read their assignment of origin of corticofugal systems upon grounds of logical probability.

grade chromatolysis following hemisection of the macaque's spinal cord were found in the giant and large pyramidal cells of area 4 (Levin and Bradford); following lesion at the rostral level of the pons (Levin and Hayashi; see also Levin, Chapter V) in the medium and small pyramids of areas 4 and 4s. But these cells were not placed in any particular layer.

The whole precentral subsector of the macaque cortex (Levin, 1936; Verhaart and Kennard, 1940; Hines, 1943) sends axons to the lateral nuclear mass of the thalamus, the subthalamic area, the substantia nigra, the pontine nuclei, and the tegmentum of the medulla oblongata. Area 6 and the posterior part of area 4 (Levin, 1936) projects upon the nucleus ruber. Areas 4 (Levin, 1936; Verhaart and Kennard, 1940) and 4s (Hines, 1943) share in the origin of the tractus corticospinalis. And as characteristic of destruction of area 4s alone (Hines, 1943) myelin degeneration was found to enter the ventral thalamic nucleus, the midbrain tegmentum, the septum pellucidum (also found by Mettler. 1935b) and the gyrus subcallosus. The precentral subsector is related as a whole to each one of the main motor masses of the brain stem, except the corpus striatum. The exact origin of the frontopallidal tract is unknown and the 4s-caudate system awaits anatomical identification.

The difficulty in analysis of the corticifugal systems from the precentral subsector is due to the fact that their axons are not found in pure culture at any place in the brain (as far as known at the present). Furthermore, analysis of corticifugal systems by the Marchi method does not always dovetail in all particulars with that by axonal reaction. Marchi degeneration demonstrated that no fibers from area 6 are found in the pyramids (Levin, 1936; Verhaart and Kennard, 1940); axonal reaction showed that no chromatolysis is found in area 6 subsequent to hemisection of the spinal cord (Levin and Bradford, 1938).

In the macaque, the Marchi method shows degeneration in the pyramids subsequent to removal (1) of the posterior part of area 4 (Levin, 1936), (2) of cytoarchitecturally discrete areas or all of the parietal lobe (Peele, 1942), and (3) of area 4s (Hines, 1943). Ablation of area 4s, also, results in degeneration in the lateral funiculus of the spinal cord on both sides and in the ventral funiculus (Hines, 1943). On the other hand, studies of secondary or axonal chromatolysis disclose retrograde degeneration in area 4 and in each area of the parietal lobe following division of the pyramid, while hemisection of the brain stem at the rostral level of the pons results in chromatolysis in areas 4, 4s, and 6 (Levin, Chapter V), but hemisection of the spinal cord at C2 causes no degeneration in area 4s (Levin and Bradford, 1938).

In man, Schröder (1914) found all chromatolytic reactions subsequent to old lesions within the internal capsule, the midbrain, the medulla oblongata, and the spinal cord to be confined to the precentral gyrus and its annectent gyri. If this were true it would indicate that the parietospinal component found in the pyramids of the macaque is not present in man. In the rabbit (Swank, 1936) the pyramids contain fibers which originate in the basal ganglia. No one, so far as the writer knows, has studied the origin of the fibers of the pyramidal tract in the chimpanzee; nor are there any Marchi studies of degeneration subsequent to surgical removals of the parietal lobe either in the great apes or in man.

Further the actual termination of even that portion of the pyramidal tract which enters the spinal cord is not known. Marchi preparations can give no more than the general site of termination. The method of degenerating boutons as studied by Hoff (1932) is not above criticism (see Barnard, 1940).[6] Leyton and Sherrington (1917) followed degenerating myelin into the ventral horn and found it to end among the cells of the motor nuclei after removal of the arm area in the chimpanzee. Schäfer (1884, 1899) did not find this in the monkeys he studied; rather he found degenerated myelin at the base of the dorsal horn and in the region of Clark's nucleus. The writer has seen black droplets[7] not only in all of these places in the monkey after ablation of area 4s or after cutting of a pyramid (Dr. Tower's preparations) but also in the intermediate area, among the cells of the intermedio-lateral column (thoracic level) and similar to Leyton and Sherrington's report among the cells of the nuclei of the ventral horn.

Axonal relationships as found in the macaque show the precentral subsector to be alike in its thalamocortical projections and its heterolateral association fibers. There are at least three zones (areas 4, 6, and 44), characterized by different homolateral association fibers and another three (areas 4, 4s, and 6) which can be differentiated upon their corticifugal connections. Area 44 has not been studied in this connection. It is highly probable that these differences in fiber relations of the precentral motor cortex were found because the architectonics of the region were recognized.

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[6] Hoff reported that he found chloral hydrate to be a better fixative than formalin. Chloral hydrate is used in histology as a macerating agent. Bodian (private communication) considers that so far all methods of fixation are so slow that no norm for boutons terminaux can be established for warm-blooded animals.

[7] [It is perhaps not amiss to call attention again to the fact that the Marchi method is very susceptible to the development of artifacts. Even when the greatest care has been taken the investigator is often most disappointed to find black droplets scattered so widely throughout the tissues as to make reliable interpretation impossible. Even in more favorable cases scattered isolated black droplets commonly have to be seen and ignored. In using the Marchi method only those findings which can be consistently confirmed in a series of animals can be accepted as reliable.—Editor.]

In Bonin's study (Chapter II) of the cytoarchitecture of the pre-central gyrus, that gyrus of man was found to be characterized by an area not found in any of the monkeys nor in the ape which he studied. This area, FA of von Economo and Koskinas or 4a of Bonin, occupies a large proportion of the arm area and about one-half of the face area. In his classification, area 4 of man should be divided into three cytoarchitecturally distinct regions, the area gigantocellularis 4γ (FAγ of von Economo and Koskinas), the area motoria simplex, 4a (FA of von Economo and Koskinas), and the area precentralis suppressoria, 4s. This area, the anterior division of area 4, was first identified by Hines (1936, 1937) as distinct physiologically from the posterior division of 4 in the macaque; for ablation of this narrow strip of cortex was followed by spasticity and inability to adduct the thigh and to abduct the toes. Later Dusser de Barenne and McCulloch (see McCulloch, Chapter VIII) called this strip of cortical tissue 4s, in both the macaque and the chimpanzee. In man area 4s is characterized by large pyramidal cells in layer IIIc (layer IVa of Bonin, see pp. 8 and 17). In the "leg" field, there are giant pyramidal cells in layer V, as well.

Bonin divides the remainder of the precentral subsector into an agranular area (6) which lies anteriorly, and a dysgranular area (44) which is to be found both anterior and ventral to the "face" field of the area gigantocellularis. The premotor area (6 of Brodmann; FB of von Economo and Koskinas; 6a of the Vogts) is differentiated from all divisions of 4 by the columnar arrangement of the nerve cells in layers III, by the smaller size of these cells, by a slightly thinner cortex, and a more pronounced stratification. The area precentralis dysgranularis (44) is characterized by the intermingling of small and large cells in layer IV, by clear-cut subdivisions in both layers III and IV, and by plainly marked off layers ii and iii. All subdivisions of 4 and 6 are unistriated, while 44 is bistriated.

Bonin, like von Economo and Koskinas, did not report the "hair sharp" boundaries of the Vogts for any of these areas. The reader gathers that the lines marked on the drawings which represent the surface of the cortex cerebri in the animals studied are as accurate as the material allows. Certainly in the writer's experience there is great individual variation from cortex to cortex even in the macaque. Nevertheless, there are throughout the cortices of primates so far studied certain similarities in cortical structure, certain similarities in corticipetal and corticifugal systems, and certain others in the intracortical connections. It seems logical then to search for certain similarities in the results of our methods of study to determine their separate contributions to function.

APPRAISAL OF THE RESULTS OF STIMULATION

Electrical stimulation of the surface of the precentral motor cortex is at best a crude method of gaining knowledge of its contribution to function. The results of such stimulations are modified not only by temperature, by blood supply, and by shock, as Sherrington demonstrated, but also by flow of cerebrospinal fluid, by the type and depth of anaesthesia, and by the type and intensity of the stimulating current (Boynton and Hines, 1933; Hines and Boynton, 1940; Tower and Hines, unpublished). The size of the unipolar electrode or the distance between the poles of the bipolar electrode determine the size of the block of cortical tissue stimulated. Consequently, all other considerations aside, the smaller that block of tissue, the simpler the movements obtained. The type and depth of anaesthesia determines within limits the corticifugal system aroused, as well as the spontaneous activity of the cortex itself (Derbyshire *et al*, 1936; Marshall *et al.*, 1937). The conditions of electrical stimulation of the cortex cerebri of mammals are not, therefore, in the strict sense comparable, unless the anaesthetic and the type of current are similar. Certainly, even in man, where the cortex can be stimulated without anaesthetizing the subject, there is no assurance that the movements obtained are the result of isolated activation of the pyramidal tract or of the activation of single nerve cells. For example, the recent results of electrical stimulation of the precentral gyrus in man (Penfield and Boldrey, 1937; Scarff, 1940) are not as similar to each other as our experience with subhuman primates would lead us to expect. It is possible that the human brain shows greater variation than brains of the subhuman primates. It is also possible that the variations are not innate but are rather the result of the conditions which put the human beings into the hands of the neurosurgeons, or, again, the result of conditions of stimulation which are not comparable. The patients of Krause were stimulated under a general anaesthesia, while those of Penfield. Scarff, and Foerster were conscious Krause used the faradic current; Foerster, the faradic and the direct current; Penfield, the galvanic, the faradic, and the thyratron; and Scarff, both the faradic current and the thyratron. As yet Bucy has not analyzed his results of stimulation of this region with the 60 c p.s. sine-wave current. That no surgeon has reported results comparable to those given by Foerster for the stimulation of the Vogts area 6aα (4a of Bonin) may be due to the fact that no one else has stimulated the precentral gyrus after the surgical separation of areas 4γ and 4a or after the interruption of the corticifugal pathways from the precentral gyrus.

Although Penfield and Erickson (1941, fig. 10, p. 46) have now given a topographical sequence as characteristic of the results of electrical stim-

ulation of this gyrus in man, so far no report from that clinic has recorded separate loci for individual muscles or muscle groups of a given extremity, except for the extensors and flexors of the fingers. On the other hand, Krause pictured such loci not only for the fingers but also for the thumb,
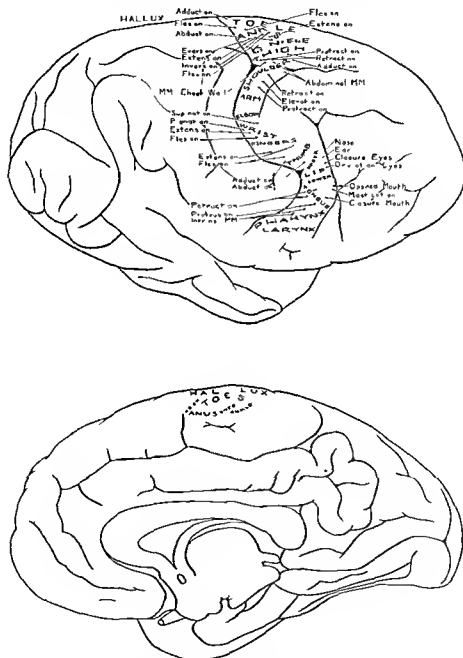
Fig. 13S—Drawings of the lateral and medial surfaces respectively of the right cortex cerebri of a chimpanzee. The musculature of the body which responded to cortical stimulation is indicated as if projected upon the precentral gyrus (a) and upon the paracentral lobule (b)

wrist, and elbow, which substantiates for the arm the description given by Foerster (1936b). A similar but less complete distribution of loci for separate movements of joints was obtained by Hines (1940) in the adult chimpanzee (fig. 138a).

In the macaque, stimulating with 60 c.p.s. sine-wave current under nembutal anaesthesia in a mosaic of points 2 mm. apart anteroposteriorly and 1 mm. mediolaterally, Woolsey (1938; private communication) defined a pattern of representation in the precentral gyrus which apparently can be analyzed in terms of basic motor arrangements of the spinal cord. In the "leg" field, between the fields for tail and trunk, muscles derived from the dorsal muscle sheet (i.e., extensors and abductors) were found represented mainly on the medial surface of the hemisphere; those derived from the ventral muscle sheet (flexors and adductors; see Hines. 1943, p 28) on the dorsolateral surface. Fewer experiments were made on the "arm" and "face" fields than on the rest of the "motor cortex," and the basic plan for the arm area still requires clarification. It appears, however, that extensors and flexors for each segment of the forelimb alternate in strips which cross the precentral gyrus anteroposteriorly. Perhaps the most important finding with respect to the "arm" field in this study is the discovery that distal parts of the arm, especially the small muscles of the hand. are represented not only in the accepted "hand" field but also in a well-defined strip through the area for the trunk and shoulder in which responses of fingers and wrist lies intermingled with those of trunk and shoulder. This strip of cortex lies adjacent to the boundary between Dusser de Barenne's "arm" and "leg" fields. At the corresponding level of the postcentral gyrus the postaxial skin field of the arm, innervated by T_1 and T_2, is represented (Woolsey, Marshall, and Bard, 1942). On the motor side, muscles of the hand and wrist are supplied in part by these same two levels of the cord. Since the hand muscles are also innervated by lower cervical levels, whereas muscles of proximal segments of the forelimb are supplied by higher cervical levels, Woolsey suggests that the findings with respect to the hand may be explained by assuming on the motor side a reversal of the cervical segments on projection to the cortex similar to that previously described for the sensory system (Woolsey, Marshall, and Bard, 1942).

Even in the face area Woolsey (1947; private communication) found that the topical localization of reacting muscles projected on the precentral gyrus is surprisingly like the mirror image of the topical localization of the skin area of the face as delimited by evoked potentials (Woolsey, Marshall, and Bard, 1942). For example, the ipsilateral motor area on the precentral gyrus lies adjacent to the ipsilateral skin area of the face on the postcentral gyrus across the central fissure.

This study indicates that in the precentral gyrus of the macaque there is a detailed pattern of representation of the skeletal muscular system and that the basic plan of this pattern can be analyzed in terms of muscles. Thus, although there is overlapping of cortical fields for various muscles and muscle groups, comparable to the overlapping of cortical fields for peripheral cutaneous areas individual muscles are represented maximally in specific parts of the precentral gyrus; just as areas of skin are represented maximally at particular points on the postcentral gyrus. This similarity in topical organization between the precentral and the postcentral gyrus suggests a special relation of afferent areas receiving cutaneous sensibility to efferent pathways leaving the cortex (Woolsey, 1947). It is just possible that further analysis of the organization of the representation of the skeletal muscular system in the precentral gyrus will discover as neat a projection of the segments of the spinal cord as has been found for the postcentral gyrus in terms of dorsal roots and dermatomes (Woolsey, 1947).

That in the macaque's precentral gyrus there is a detailed pattern of representation of the skeletal muscular system and that the basic plan of this pattern can be analyzed in terms of muscles has been confirmed for the muscles acting upon or over the ankle joint. In a meticulous study Chang, Ruch, and Ward (1947) recorded myographically the simultaneous responses of eight muscles. During a systematic exploration of the dorsolateral surface of the precentral gyrus of nine macaques the contractions of these eight individual muscles were isometrically recorded and their relative threshold, latency of response, and tension-ratio were recorded.

When the stimulating current was near threshold value, a focus was found for all the muscles acting over or on the ankle joint except the m. peroneus longus. (Woolsey found the focus of this muscle on the medial surface.) The focus of representation for any two of the eight muscles attached to the myograph was never discovered at exactly the same locus although the fringes around contiguous foci for different muscles overlapped to a greater or lesser extent. No manipulation of the stimulating current on these fringes was able to produce solitary responses. Also, there were silent areas for the muscles attached to the myograph.

Furthermore, the points yielding the shortest latency clustered in a restricted focus while those of long latency were on the fringe. The foci of shortest latency corresponded to those which yielded solitary responses. That is, the foci which yielded solitary responses were also characterized by a minimal latent period; those which yielded multiple responses, by a longer latent period. When several muscles responded to the activation

of a cortical focus for a particular muscle, the tension-ratio of that muscle was always stronger than for that of any of the other muscles responding.

The details of this study not only support the analysis of Woolsey, but also demonstrate that it is possible to elicit topical motor activity without a concomitant of topical inhibitory activity. Moreover, Bosma and Gellhorn's (1946) electromyographical studies of response of antagonistic flexor and extensor muscles to stimulation of the "motor" cortex show that these muscles (in cat and monkey) under certain conditions can be caused to contract simultaneously without an initial phase of inhibitory activity within the opposing muscle. Therefore, without evidence of the reciprocal innervation of Hering and Sherrington (1897), which Walshe (1946) considers to be "the essence of motor response to cortical activity," contraction of single muscles and coinnervation of opposing muscles can be elicited by stimulation of this cortical tissue.

That Leyton and Sherrington did not find such loci may be due to the type of electric current used for stimulation. Whereas the sine-wave current can be controlled and the frequency and intensity made to remain constant, the frequency and the intensity of the faradic current varies from time to time. Hines and Boynton (1940) found (1) that the peculiar resemblance "to life" of the movements elicited by stimulation with the sine-wave current were not obtained either with the faradic current or with the square wave, and (2) that there was an optimum frequency with the sine-wave current. Utilizing square-wave currents the threshold was lower with 60 c.p.s. than with 59 c.p.s., and the former elicited isolated movements but the latter did not. The results of electrical stimulation of the precentral gyrus do not demonstrate the ability of that region to produce movement per se; rather, they illustrate what the neuromuscular mechanism can do when a current of particular form and intensity is applied to the cortical surface. Undoubtedly variations from individual to individual exist. Certainly some minute type of anatomical localization must be present. Some of the variations reported by neurosurgeons must be due to the current used and some may possibly be the result of analysis.[6]

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[6] There is great difficulty in evaluating the results of electrical stimulation of the precentral gyrus of man for comparison with those of the more exhaustive explorations of the homologous area in laboratory primates. Neither Foerster nor Penfield and Boldrey give the individual protocols from which their conclusions were drawn. And although both Krause and Scarff list the results of their electrical explorations of the precentral gyrus, the number of points stimulated within any one particular area are so few that little can be known about the total capacity of the region so investigated. Further, unless the observer knows something about the muscles whose contraction produces the movement recorded, the scientific value of the record is indeed slight. For example, in Penfield and Boldrey's report (1937, p. 415) metacarpophalangeal joint movement has been described regularly as "movement of the hand." These joints can be flexed by three different muscles—the flexor digitorum sublimis, the flexor digitorum profundus, and the interossei.

In résumé, besides the elicitation of contraction of single muscles or parts of single muscles, that of either extensor or flexor sheets of muscles was obtained as well as coinnervations involving both flexors and extensors. The coinnervations resembled the patterns of movements in use by the particular animal in question (Hines and Boynton, 1940, for the macaque; Hines, 1940, for the chimpanzee). These movements never survived surgical division of the pyramids (Tower and Hines, unpublished, macaque). What did survive this procedure were synergic movements, ipsilateral, contralateral, and bilateral, which frequently reached the scope of acts.

Hering's (1898) method of analysis of one of the use patterns common to all primates showed that that locus which yielded the whole movement would, under given conditions, yield a part. Hering determined the point on the precentral gyrus of a monkey (species not given), electrical stimulation of which yielded flexion of the fingers and extension of the wrist. He cut the flexor digitorum communis tendon. Upon restimulation of the point, extension of the wrist was elicited. In another animal the tendons of the extensores carpi radialis longus and brevis were severed. Stimulation of the locus which had given the whole movement now yielded only flexion of the fingers.

The summed picture of reactive points published by Penfield and Boldrey (1937), representing loci which yielded motor responses to the application of the electric current, showed that only a few of these points transgressed the anterior border of the precentral gyrus. Further, these points were definitely more dense in the posterior division of this gyrus. Nevertheless, many were located not only in area 4a but also in area 6. Comparison of the line drawn for the anterior border of area 4 either by Campbell, Brodmann, or Buey with the limit of the reactive points in the adult chimpanzee's precentral gyrus (Hines, 1940), shows that area 6 yields contraction of isolated movements. This was particularly true of the face area. But if the reactive points of lowest threshold be outlined on this gyrus in the arm and leg areas, then the majority of them fall within some part of area 4 (of Bonin). No attempt was made in these stimulations to use the electric current to differentiate the boundary of area 4 from that of area 6.

In the macaque (Hines, 1937) it is possible to determine with some degree of accuracy the border line between areas 4s and 6. If the sine-wave current is kept at threshold value, a line can be drawn just anterior to the dorsoventral row of points from which isolated movements of the contralateral proximal part of the leg (dorsal to the superior precentral fissure) and of the arm (ventral to this fissure) were elicited. The cortical tissue

The Precentral Motor Cortex

anterior to this line will show the architecture of area 6, and that posterior to it the structure of area 4.[*] This was observed in all the brains from which area 6 was removed. This line has to be determined for each brain at the time of operation, for it is not possible to draw a picture of the surface markings of the cortex cerebri of the adult brain of this primate and trace thereon an anterior boundary for area 4 which will hold true for each individual of this species. However, if the faradic current is used, the excitable cortex transgresses upon the posterior border of area 6 in the macaque just as Campbell described for the chimpanzees stimulated by Leyton (or Grünbaum) and Sherrington.

Results of Stimulation of Area 6

In man, Foerster (1931, 1936b) reported that faradic currents of high intensity elicited from area 6 (his 6aβ) rotation of the head, eyes, and trunk to the opposite side, as well as complex synergic movements of flexion or of extension of the contralateral arm and leg, even after areas 4 and 6aα (4a of Bonin) had been removed. If the writer understands Penfield and Erickson (1941) correctly, they have produced similar movements in man only when there was an epileptic after-discharge present, and never as a simple cortical response. No such explanation can be offered for the results of stimulations of a few points in the homologous region of the chimpanzee's cortex. These points yielded contraction of proximal muscles of the arm or of the leg and rather simple synergic movements with 2.0 mA or less of the sine-wave current (Hines, 1940). In the macaque, with both pyramids cut, stimulation with this current of the anterior division of area 4 and the posterior division of area 6 elicited both diagonal movements (one arm and the contralateral leg) and synergic movements of flexors and extensors; when the anterior division of area 6 was stimulated, flexor synergies with grasping and conjugate deviation of the eyes, head, and trunk to the opposite side were obtained (Tower and Hines, unpublished).

Kennard (Chapter XI) has outlined the changes in autonomic function which result from stimulation of this area. Not only were contractions of gastric musculature recorded, but also changes in kidney volume. On the other hand, in man, Penfield and Boldrey (1937) found no evidence of gastrointestinal response to stimulation of the cortex. Conjugate movements of the eyes in man were found by Erickson (Chapter XIII) to be the result of stimulation of area 8, not of any part of area 6, in contrast

[*] In spite of the greatest care possible to leave the remaining cut surface of the cortex with an adequate blood supply, there is some slight degeneration at this border. This degeneration may account for the fact that the region left behind always proved to be area 4

with the observations of Smith in subhuman primates (cf. Chapter XII). Adversive movements were obtained only from the face field. Below this region in 6b (area 44 in the present study) Foerster (1931, 1936) reported that electrical stimulation produced rhythmic coordinated movements of musculature innervated by the Vth, VIIth, IXth, Xth, and XIIth cranial nerves which outlasted the electrical stimulation.

Phenomena Other Than Movement—Electrical stimulation of the human precentral gyrus (Penfield and Boldrey, 1937; Penfield and Erickson, 1941) has produced only one type of "sensation," the desire to move. Relaxation of tonic innervation has only recently been reported (see page 380). No one has described the reciprocal innervation of Sherrington; possibly because no one has sought it. In the macaque stimulation of the surface of the precentral subsector with the sine-wave current was followed by inhibition of tonic innervation of skeletal muscle, under light ether anaesthesia. With the pyramids intact a topical inhibition of tonic innervation was elicited by stimulation of any part of the whole of area 4. With the pyramids severed topical inhibition of tonic innervation disappeared, but a non-topographical one remained, effective bilaterally.[10] Stimulation of the anterior division of area 4 (4s) acts strongly to relax standing tone, while this and the posterior part of area 6 relax flexor tone (Tower and Hines, 1935, and in preparation).

Development of Excitability of the Precentral Gyrus in the Infant Macaque

The maturation of the precentral gyrus in the infant macaque, when read in terms of movement and other phenomena, such as relaxation of tone, tonic innervation, and fixation, elicited by electrical stimulation of its surface, proceeded in an orderly manner (Hines and Boynton, 1940) The non-pyramidal type of movement, holokinesis,[11] was obtained before birth in fetuses of 66 to 125 days gestation age; the pyramidal type, idiokinesis,[11] in those of 135 to 162 days gestation age (fig. 139). The reactive points for idiokinesis were situated posteriorly in the three topographical regions of this gyrus. Surrounding these points, loci were found which

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[10] The writer was forced to use the term inhibition in this case, because so far it has been impossible to know exactly what type of inhibition the electric current had aroused.

[11] The terms holokinesis and idiokinesis were used by Hines and Boynton (1940) to distinguish between two general types of movements elicited by stimulation of the precentral gyrus of the infant macaque with sine-wave currents. The simple contralateral movements which cannot be elicited after surgical division of the pyramids were called idiokinetic movements, i.e., idiokinesis. Movements which were obtained before the pyramidal tract had developed, which were either bilateral in scope or without topographical localization, or which survived surgical division of the pyramids, were classified as holokinetic movements, i.e., holokinesis.

yielded holokinesis, and relaxation of tone (chalasis) and sometimes tonic innervation of skeletal muscle. After birth, as growth proceeded (fig. 140), idiokinetic movements were elicited from more rostrally lying points. On the interregional face and arm, and arm and leg borders, holokinesis and chalasis gave place to idiokinesis, until at four months of age holokinesis and chalasis were easily obtained only from the rostral border of the precentral gyrus. Nevertheless, special manipulation of frequency and intensity of the stimulating current elicited both holokinesis and chalasis from an idiokinetic point. Although the difficulty of elicitation of phenomena other than idiokinesis increased with age, nevertheless, nonpyramidal units could apparently be activated by stimulation of this cortical surface.
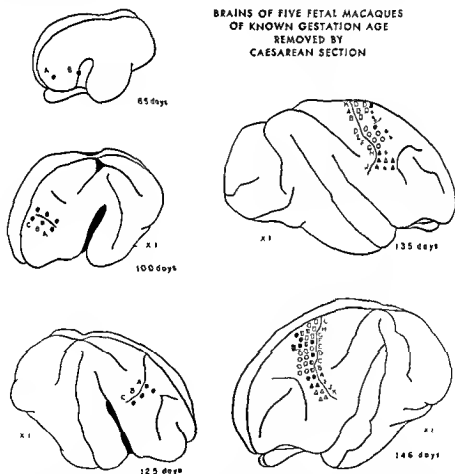
FIG 139—Outline drawings of the cortex cerebri of 5 fetal macaques, showing the areas from which the sine-wave current was able to elicit movement of skeletal muscle and to affect either tone within striated muscle or respiratory movements. The key to the symbols is given in fig 140 (from Hines and Boynton, 1940).

Before birth, the results of stimulation of the precentral gyrus bore little relation to observed activity. No progression was possible for the fetus removed by Caesarean section, yet diagonal progression was elicited by stimulation. No isolated movements of the digits were observed; yet they were obtained by cortical stimulation. After birth, during the first two weeks of life, a closer correspondence between observed activity and
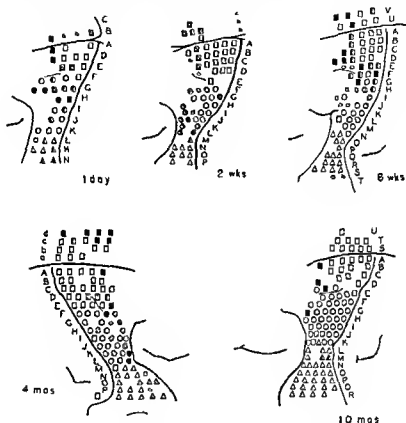
PRECENTRAL GYRI OF FIVE INFANT MACAQUES

LEG	ARM	FACE	
□	○	△	PYRAMIDAL TYPE OF MOVEMENT.
■	■	▲	EXTRAPYRAMIDAL TYPE OF MOVEMENT.
▣	◐	◮	COMBINATION OF BOTH TYPES
	•		RELAXATION OF TONE.
	◦		FIXATION.
	◌		EYES
	▮		EYES & EXTRAPYRAMIDAL MOVEMENT.

Fig. 140—Outline drawings of the precentral gyrus (paracentral lobule also indicated) of five infant macaques, showing the areas from which the sine-wave current was able to elicit movements of skeletal muscle and to affect either respiration or tone within striated muscle. The key to the symbols is appended to the figure and is self-explanatory (from Hines and Boynton, 1910).

the elicitation of movement by cortical stimulation was obtained. To be sure, isolated movements of the digits were elicited, though they were not observed in the infant's use of either his fingers or his toes, but other elicited idiokinetic movements followed the animal's use patterns. Conservations of the tail and thigh muscles were elicited, and movements of the tail occurred with those of the lower extremity. Progression, parts of the nursing pattern, and rhythmical movements were caused by cortical • stimulation and were seen as a part of the particular animal's activity.

From the age of one month to one year, the use patterns and the idiokinetic movements elicited by electrical stimulation of the precentral gyrus showed a surprisingly close, although not exact, correspondence with the use patterns and the progression patterns as they appeared in the infant macaque. Further, there was a relation between manner of use of the extremities in progression and in manipulation of an object, and the disappearance of resistance to passive movement. For example, protraction of the arm and retraction of the leg beyond a 90° angle with the trunk, even in progression, was not observed before five weeks of age, or until resistance to passive protraction of the upper extremity (beginning after four weeks of age), and to passive retraction of the lower (beginning at three weeks), had markedly decreased. Protraction of the arm and retraction of the leg as idiokinetic movements were never obtained by stimulation of the precentral gyrus before six weeks of age. Again, resistance offered to supination by the tone in the flexor carpi ulnaris and the pronators began to decrease at four weeks of age, and did not become normal until ten weeks. Stimulation of area 4 never elicited isolated supination of the forearm until the fifth week. In this case, isolated supination of the forearm was caused by electrical stimulation seven weeks before it was observed to be accomplished by the infant himself. The fact that cortical stimulation did not elicit protraction of the arm, retraction of the leg, or supination of the forearm until after resistance offered by their respective antagonists decreased suggests a correlation of maturation of the non-pyramidal chalastic "mechanism" with that of development of pyramidal initiation.[11, 12]

Fixation was also obtained earlier by electrical stimulation than it was observed normally in the young monkey; and by the same means muscles which later in development were caused to be fixed, were earlier actively contracted both by the electric current and by the animal himself. In many

[12] It is interesting to note that these three movements are among those which suffer severely in the adult macaque subsequent to the removal of the precentral gyrus. Contralateral to the ablation resistance is increased to passive retraction of the leg, to passive protraction of the arm, and to passive supination of the forearm, and in bipedal progression, protraction of the upper extremity and retraction of the lower extremity does not occur, and isolated supination of the forearm has never been observed.

instances fixation of muscles proximal to the ones which contracted was elicited from cortical points located for the active movement observed.

Chalasis and tonic innervation were also caused by cortical stimulation. They were obtained after section of the pyramids. Diagonal progression and parts of gallop progression were elicited by stimulation of both area 6 and area 4, both before and after section of the pyramids. Moreover, these progression patterns and chalasis were obtained from immature cortices before the loci stimulated yielded idiokinetic movements.

Besides these movements, initiation of the nursing pattern and of the infantile defecation pattern were also obtained by cortical stimulation only during the period in which they were present in the animal's behavior. When one pyramid was cut before regression of the nursing pattern had taken place, the extremity opposite the lesion continued to use that pattern for several weeks after it had disappeared in the homolateral extremity. The defecation pattern, however went through its usual development and regression, except that after the pyramid was cut the tail was never as greatly dorsiflexed as in the normal infant (Hines, 1942).

These findings indicate that the contribution of the precentral gyrus to the motor activity of the growing monkey cannot be read in terms of the maturation of a single corticifugal projection unit. Although the pyramidal unit appears to lower the threshold (i.e. the intensity) for the stimulating current, to aid in fixation of proximally lying muscles, and to initiate both "isolated" and cooperating movements, there are activities which can be caused by electrical stimulation of the precentral gyrus in which it takes no part. Certain types of holokinesis, chalasis, and tonic innervation are independent of its activity. When the results of stimulation of the precentral gyrus, as well as those of the region lying anterior to it (6), are compared with the development of motor activity in the infant macaque, a certain integration seems to characterize this region during each step in development. The activity which characterizes the young of this species at any viable age is modified during each phase of its development by the activity of this cortical region.

Conditions of Excitation of Corticifugal Pathways

It is evident that nervous impulses produced by electrical stimulation of the precentral motor cortex are transmitted to motor nuclei of the brain stem and spinal cord by two general types of fibers, (1) those found within the medullary pyramids, and (2) those not found there. The electric current may reach these corticifugal systems via a physical spread of current through the cortical lamina or by the synaptic relations of inter- and intra-regional axones. Suprathreshold stimuli with a minute unipolar

electrode or threshold stimuli delivered either by a broad unipolar electrode or by a bipolar electrode (Hines and Boynton, 1940) increase the number of efferent fibers activated and do not allow the observer to distinguish between movements transmitted to the cord via pyramidal and extrapyramidal units.

However, comparison of movements elicited by electrical stimulation of the "motor" cortex of the normal animal with those of the pyramidal animal demonstrate that some of those which have been observed in the normal and considered to be pyramidal were frequently a combination of the activity of both units (Tower, 1935, 1936). In the intact macaque (infant, Hines and Boynton, 1940; adult, Tower and Hines, 1935; and unpublished) the extrapyramidal type of movement, in contrast to the pyramidal, cannot be obtained after shock, after interference with cerebral circulation, under morphine, or under any anaesthesia except the lightest. Non-topical inhibition of tonic innervation (extrapyramidal), on the other hand, was not as susceptible to shock or to interference with cerebral circulation as were the extrapyramidal types of movement, and could be elicited in the pseudo-decerebrate stage (Tower, 1933; Tower and Hines, in preparation). The threshold intensity of the sine-wave current used as stimulus was occasionally less for the relaxation of tonic innervation than for pyramidal movements and always less for pyramidal movements than for extrapyramidal movements in the monkey (Tower and Hines).

Consequently, stimulation of the precentral motor cortex either in conscious man or in animals with supraliminal stimuli fulfills some of the conditions for evoking extrapyramidal movements. Is it unreasonable to consider that some of the movements yielded by the precentral subsector in conscious man may reach the motor nuclei of the brain stem and spinal cord via extrapyramidal pathways as well as over nerve fibers which lie in the pyramids? Moreover, is it not to be anticipated that suprathreshold stimulation of the precentral gyrus of any animal would elicit a multiplicity of responses, delivered to the segmental nuclei via both the pyramidal and extrapyramidal pathways?

Murphy and Gellhorn (1945) obtained movements of the various joints of the extremities and of the muscles of the face in co-extensive areas and found considerable overlap between the leg and arm or the arm and face subdivisions. The loci which yielded these movements of the extremities resembled the loci from which holokinetic movements were elicited from the precentral gyrus of the infant macaque (Hines and Boynton, 1940).

It is the topical contraction of skeletal muscle, i.e., the solitary response of Chang, Ruch, and Ward, the coinnervations of flexors and extensors observed in use patterns, the fractionization of extensor or of flexor sheets, and the reciprocal innervation aroused at the cortical level which disap-

pears after the pyramids are surgically severed Thereafter, no one of these
activities of skeletal muscle can be elicited by stimulation of the cortical
surface of the precentral subsector Non-topical contraction of skeletal
muscle and non-topical changes in tone of skeletal muscle remain.

RESULTS OF REMOVAL OF THE PRECENTRAL
MOTOR CORTEX

The ablations of the precentral motor cortex so far reported for man
are, with rare exceptions, not confined to a single cytoarchitectonic area.
It is conceivable that some of area 6 could be removed without injury
to any part of either area 4 or 8 Area 4 of the leg region has been taken
out without extensive injury to contiguous areas, but in the "leg" area
of man, area 4 is not as clearly divisible into areas 4γ, $4a$, and $4s$ as it is in
the arm area (cf. Chapter II). To expect chance to allow the neurosurgeon
opportunity to excise only area $4a$ or 4γ in the arm area is to trespass
upon the ground of probability, and yet Kleist generalized as if lesions
were confined to the Vogts area $6a$, an area part of which included Bonin's
$4a$. Discrete removal of area $4s$ in man will probably never occur. Never-
theless, that region might be taken out of the chimpanzee's cortex with
almost as much ease as in the macaque.

Area 6

Kleist (1934), and Foerster (1936b) seem to be the only ones who have
reported the results of lesions confined to area 6.[18] Both described difficulty
in turning head and trunk to the opposite side, and in stopping movement.
Foerster found that movements of the contralateral extremities were slow
and that both sequential acts and rapid, alternating movements were
poorly performed. Neither listed the grasp reflex Apparently, in man the
medial surface of this region has to be injured for the grasp reflex to appear
(Schuster, 1927). In the macaque removal of area 6 alone does not change
the distribution of tone in the muscles, nor modify tendon reflexes; rather
it is followed by the grasp reflex in the opposite extremities (stronger and
more enduring in the hand than in the foot). When area $4s$, however, is
added to the lesion (Hines, 1937; 1943) tone is so great at first in both
extensors and flexors of the second joint that sitting is impossible and,
later, climbing the mesh of a cage is accomplished slowly and with obvious
effort. The tendon reflexes are brisk and irradiating, but the resistance to
passive movement is not clasp-knife in type. In man, according to Ken-
nard, Viets, and Fulton (1934), destruction of area $6a$ (of the Vogts) re-

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[18] Area $6a$ as utilized by Kleist and Foerster and described by the Vogts corresponds to
areas $4a$, $4s$, and 6 of this monograph (cf. Chapter II and the frontispiece).

sults in spasticity. As noted previously,[12] however, the Vogts area 6a includes area 4s. Kleist (1934) reported that apraxia of movement, with subsequent "restitution," followed lesions of the Vogts area 6aα (our area 4a).

The Precentral Gyrus

Hughlings Jackson's concept of dual loss as the result of lesions of the central nervous system is peculiarly applicable to the sequelae of injury to the precentral gyrus. The functions lost are the discrete movements of the extremities opposite the lesion; the functions released are hypertonus and clonus, the briskness and irradiating quality of the tendon reflexes, the exaggerated character of the tonic reflexes of muscular and labyrinthian origin, associated movements, and the positive Babinski. Besides these, two other changes in muscle frequently occur, atrophy and contracture.

The Function Lost—In the normal individual, the muscles used to achieve a desired objective have been classed by Beevor (1903) as prime movers, synergic muscles, fixers, and antagonists. For example, simultaneous flexion of all the fingers is accompanied by extension of the wrist. The cooperating muscles (Beevor's synergic muscles) are the extensors of the wrist. If the subject attempts to increase the flexion of the fingers not only does the wrist become more extended but the extensors of the fingers also can be felt to contract, and palpation of the proximal muscles of the arm will demonstrate that they have become firm and taut. The fixation of the more proximally lying muscles has in the meantime increased. Further, if the flexion of the fingers is very great the extensors of the neck and the adductors of the scapula will also become firm. Any one particular act contains similar parts; that is, discrete or isolated movement of distal musculature when used in the performance of skilled acts is accompanied by a cooperating movement of more proximal muscles, a fixation or holding contraction at the girdle with fixation or cooperating movements at the middle joint, together with an easily modified holding contraction of the muscles which act as antagonists to the prime movers. Simple as this picture appears to be, the descriptions of the results of partial or complete ablations of the precentral gyrus are not written in such a manner that the reader can analyze adequately the loss suffered by the various muscles used in skilled performance.

Hughlings Jackson observed that subsequent to injury to his "middle level" the innervation of the affected extremity flowed down the limb, that is, the initiation of movement took place in the proximal muscles. And that is also true for the monkey which has suffered a comparable lesion, as well as for the normal infant monkey (Hines, 1942).

The increase in frequency of ablation of the whole or part of the precentral gyrus and its annectent convolutions for the purpose of halting either convulsive seizures or abnormal uncontrolled movements should give sufficient data for the adequate analysis of the motor loss which always follows. None of the recent reports give an adequate picture of the manner in which the patient uses the muscles to perform a given act. Penfield and Erickson (1941) report that if the hand area is completely removed, "the hand becomes completely paralyzed for any skilled movement whatever." And yet a similar but more radical operation (whole arm area) performed by Horsley (1909) left the individual with the ability to toss a tennis ball into the air in a sufficiently accurate manner for him to be able to play the game (see Head, 1920, p. 626). Again (Penfield and Erickson), "if the removal is small, the delicate movements of the fingers and thumb disappear although movement of all the digits together as in flexion or extension and movement of wrist, elbow, and shoulder may be produced." Foerster (1936c) described a similar isolated lesion as resulting in similar circumscribed loss of control of skeletal muscle, but with systematic training the boy, from whom the hand-finger area had been excised, learned "to oppose the thumb in a perfectly correct way." This movement however was always accompanied by a similar movement of the opposite normal thumb. Buttoning and writing with his right (affected) hand was accompanied by homologous movements of his left or normal hand. But most remarkable was the report of the man, who at autopsy showed a complete degeneration of the left pyramidal tract in the medulla, who before training could perform only the stereotyped extrapyramidal synergies of the arm, and who learned to hold a pencil correctly and to write. Bucy's Case 1 (p. 358), from whom the uppermost part of the precentral gyrus and the paracentral lobule were removed, was able to skate, hike, and dance before the first post-operative year had passed. Apparently topical localization is so discrete that paralysis of the shoulder, upper arm, and forearm can exist without any implication of the muscles of the hand or fingers (Foerster, 1936c). And yet there is no analysis of the movements which remain after injury to the precentral gyrus which takes into consideration the whole series of complex activity of the muscles involved in the performance of discrete movements in normal man. We do not know whether Bucy's patient was able to cut inner and outer circles with the right leg, nor do we know whether fixation of the proximal muscles (which were reported paralyzed) accompanied the use of the uninvolved muscles of the hand and fingers of Foerster's patient.

Judging by Marinesco's description (1903) of the method by which his patient picked up and held an object a year after removal of the precentral gyrus, fixation of proximal muscles and the cooperating extension of the

wrist and partial pronation of the forearm had disappeared. Initially the sequence of muscular contraction used by Foerster's patients must have resembled that of Marinesco's, for they were unable to isolate either the flexor or extensor synergies. What would be interesting to know is what happened in the proximal muscles after these patients had learned to write. How did the loss of a part of the precentral gyrus affect the whole act? Was loss of fixation associated only with loss of upper arm and pectoral girdle representation? How normal was fixation of these muscles after the cortical representation of hand and fingers was removed; was the effect of such a lesion confined to cooperating muscles and prime movers?[1]

Certain varieties of skilled movements, especially those used in playing games or those of the cooperating extremity in the performance of skilled movements by the active extremity, are initiated proximally in the girdles or in the muscles attached to the girdles In the sense of Foerster they resemble in pattern extrapyramidal movements of extension or of flexion, with the important difference that they are not stereotyped. This ability to utilize parts of the stereotyped proximally initiated movement is also lost with the loss of the precentral gyrus.

In the clinical condition of spastic paralysis, maximal paralysis is differential in its distribution. That a part of this differential distribution depends upon the differential distribution of hypertonus was shown by Foerster's (1936b) combination of partial resection of nerves and lengthening or transplantation of tendons. These opérations enabled patients to elevate, protract, and abduct the upper arm, extend the elbow, and supinate the forearm, or to abduct the thigh, dorsoflex the foot, and flex the knee But the paralysis of the retractors of the thigh remained. The difficulty in extension of the fingers may in part be due to the contracture of the flexors of these digits, for in removals of the arm area alone, the fingers can be flexed and extended in unison.

Contracture cannot, however, account for the total picture of the differential loss described for this condition. In the monkey, the differential impairment of movement of skeletal muscles subsequent to removal of

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[1] "These questions might be answered in large part if studies similar to those of Beevor (1903) were made upon humans from which subdivisions of the precentral gyrus had been removed Beevor studied a case of hemiplegia in which "the return of power" had commenced in the hand The patient had "no power" to extend the wrist or to flex or to extend the elbow, and yet when requested to grasp with full strength the flexors of all the fingers contracted (prime movers in Beevor's terminology), then the extensors of the wrist (synergic muscles), followed by fixation of the triceps muscle, when the flexion of the fingers had reached a certain strength

On the contrary, Hering (1898) concluded that both the cooperative movements he studied (flexion of fingers and extension of wrist; extension of fingers and flexion of wrist) were injured in hemiplegia, but that the power of hand closure although less than normal remained proportionately greater than that of opening of the hand

area 4 (Hines, 1943), in which contracture was found, was strikingly similar to that which followed surgical division of one pyramid (Tower, 1940). In both, initiation of movement in the protractors, elevators, and adductors of the upper arm and in the retractors, external rotators, and adductors of the thigh was just as impossible as that of selective flexion, extension, abduction, or adduction of the digits. Neither isolated supination nor pronation of the forearm nor ulnar or radial flexion of the wrist were observed. Similarly at the ankle no discrete contractions of the dorsoflexors or evertors were seen. The remaining extrapyramidal projection systems did allow, on the other hand, some apparently discrete retraction and abduction of the upper arm and some protraction and abduction of the thigh. In both conditions, cooperative movements were slowly and incompletely performed; their threshold was raised, but their basic pattern remained unaltered.[15] Only when the areas for the extremities were removed bilaterally was this basic pattern altered. The use of skeletal muscle by such an adult monkey resembled in detail that described for Marinesco's patient.

It is common experience of both the experimental neurologist (cf. Kennard, Chapter IX) and the neurosurgeon that loss of the peculiar selective control of movements just described which follows well circumscribed lesions of cortical loci in which a part of an extremity is represented is never as debilitating to the part as loss of a larger area which includes the representation of more of the extremity. This condition may be due in part to loss of fixation in more proximal muscles. Again, the loss of control of musculature of one extremity is never as severe in unilateral lesions of the representation of that extremity in the precentral gyrus (foot area, Fulton and Keller, 1932) as it becomes when the lesion is bilateral. Here the incidence of loss affecting distal musculature is little modified; rather the degree of loss is increased in the proximal muscles, not the selection of muscles. Although Penfield and Erickson did not detect any change in the control of trunk and neck musculature after unilateral removal in man, nevertheless, Beevor's (1909) analysis of movements of the trunk in a case of left-sided hemiplegia showed that the muscles of the right trunk were paralyzed or weak when they acted in right-sided movements, while those of the left trunk acted normally in right-sided movements. When the two sides acted together the power was equal, but the muscles on the left contracted later. In the monkey, after bilateral removal of the leg and arm divisions of area 4, the axial extensors never again hold the trunk erect.

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[15] This analysis of the loss suffered by the monkey subsequent to these two lesions is the result of three types of observations, namely, that of the use of muscles in self-initiated acts, that of their use in attempts to obtain desirable objects offered by the examiner, and that of their use in the stepping, hopping, and placing acts. The monkey is not therefore as ideal an animal for such analysis as man would be.

The Functions Released—The functions released can in part be classified as sequelae to interruption of the corticifugal pathways of the frontal lobe at certain levels of the central nervous system. Excision of area 4 in the monkey, or subdivisions of area 4 alone in man (Walshe, 1935; Sachs, 1935) or interruption of descending pathways (1) at the level of the pons in the monkey (Tower, 1940), and (2) within the lateral funiculus of the spinal cord in man (partial Brown-Sequard syndrome) and in the monkey, are followed by hypertonus, clonus, brisk and irradiating tendon reflexes, and associated movements. When interrupted above the level of the vestibular nerve, exaggerated tonic reflexes may be added. Given time, contractures of certain muscles appear, and in many cases atrophy also. If, however, the lesion in the monkey (Wagley, 1945) is confined to the ventral division of the lateral funiculus, hypertonus, brisk, irradiating reflexes, and tremor follow and if to the ventral funiculus, only clonus and brisk tendon reflexes Associated movements were not observed. If the animal is man or the chimpanzee, the Babinski reflex will be positive. On the other hand were the interruption of corticifugal pathways confined to the ventral division of the lateral funiculus, hypertonus, brisk, —see Tower's report of Hausman's case, Chapter VI), only two of these released functions would appear, associated movements and the sign of Babinski; in the macaque, associated movements only. In both atrophy is observed. It would seem, then, that associated movements are the expression of activity of the descending pathways which do not pass to the spinal cord within the pyramids.

Hypertonus and Associated Release Phenomena—In the monkey the results of excision of the anterior border of area 4 differ from those of removal of the posterior part of area 4; for with the former ablation the functions released were dominant, and with the latter, those of loss. Subsequent to the removal of the anterior border of area 4 (4s) the permanent residual paralysis was confined to the inability to initiate adduction of the thigh and abduction of the toes; and of the posterior border of area 4 (4γ), to the inability to initiate retraction and adduction of the thigh, and to grade the flexion or extension of the digits or to abduct or to adduct them, as separate movements. After the 4s ablation a differential muscular hypertonus was present from the first day; after the 4γ ablation tone was decreased in all muscles opposite the lesion for months. When area 4s was removed, the tone in the contralateral extremities was maximal in the flexors of the elbow, the ventral and ulnar flexors of the wrist, the retractors of the upper arm, the extensors of the knee, the ventriflexors and invertors of the foot, and the protractors and adductors of the thigh. The "clasp-knife" quality of hypertonus was demonstrated as resistance to passive stretching of the quadriceps femoris or of the biceps brachii during

the middle 30 to 40 degrees of respective flexion or extension. All tendon reflexes examined (10) in the limbs opposite the lesion were brisk. Irradiation to more proximally lying muscles accompanied action of the flexors of the ankle, toes, and fingers. The extensors of the knee recruited the contralateral adductors of the thigh. Clonus was elicited by sudden stretch, or was observed to accompany sudden, quick movements initiated by the animal. In contrast to this picture in the macaque from which 4γ only had been removed, all tendon reflexes, except that of the contralateral quadriceps femoris, were not brisk, and did not irradiate. No method of stimulus which was tried produced clonus, and none was seen in the monkey's self-initiated movements. The combined ablation of these two areas (4s and 4γ) produced the paralysis which was described as following the ablation of 4γ, and all the phenomena of release which characterized the removal of 4s. The appearance of the phenomena of release, however, was frequently delayed for a few days. It is obvious that the results of removal of the posterior division of area 4 were similar to the reports of Fulton (1934a) as that of the whole of area 4.

On the other hand if Brodmann's area 6 was removed (Richter and Hines, 1934) no sign of paralysis was visible, nor was any change in quantity or distribution of tone observed. The tendon reflexes were neither brisk nor quick and they did not irradiate. No clonus was initiated by sudden and maintained stretch. Rather this operation produced a well-developed grasp reflex in the hand (transient in the foot) of the contralateral extremity—a response initiated by pressure upon the interdigital pads and maintained by stretch upon the flexors. It is patent that the results of this operation in the monkey do not simulate those reported subsequent to lesions confined to the homologous area in man's cortex ($6a\beta$, Vogts; 6, Bonin; see Aring, Chapter XVI).

Rather, the results of this lesion in man resemble more closely those of the combined lesion of areas 6 and 4s in the macaque. For in the macaque the outstanding sequela was a hypertonus which had the quality and distribution of area 4 lesions distal to the second joints of the extremities; but proximal to that joint the hypertonus was distributed in both the flexors and extensors alike. At these joints the resistance to passive movement was steady and similar throughout the excursion. The positive supporting reaction remained markedly exaggerated contralateral to this lesion for years. And the difficulty in making alternate movements slowed all movement.

Therefore, only one of the phenomena of release which follow excision of the precentral gyrus of primates appears invariably after cutting the corticifugal systems which pass through the medullary pyramids—associated movements (and the positive Babinski, in the chimpanzee). And

since it is possible in the monkey to produce three of these phenomena with minimal paralysis by the removal of 4s, is it not justified to consider that the hypertonic group of sequelae are released by the removal of descending pathways which do not pass through the medullary pyramids? Indeed, a cortico-bulbo-reticular pathway from 4s (macaque) has been identified (McCulloch, Graf, and Magoun, 1946) as occupying a "suppressor" region in the medial reticular formation at the level of the pons (Ward, 1947); and Wagley (1945) has reported that interruption of pathways in the ventral division of the lateral funiculus or in the ventral funiculus without injury to the corticospinal tracts was followed by some of the phenomena of release.

· **Atrophy**—In this monograph Davison (Chapter VII) has reported that he found no atrophy of skeletal muscle to follow lesions anterior to the central fissure, while on the contrary Bucy (Chapter XIV) has. Tower described atrophy of skeletal muscle contralateral to pyramidal lesion in both the macaque (1940) and the chimpanzee (Chapter VI) and quotes Hausman as finding it in his case of suspected pyramidal lesion in man. In this type of lesion the greater wasting characterized the distal musculature of the extremities; whereas, interruption of the extrapyramidal pathways in the spinal cord (macaque) was followed by a greater wasting of the proximal muscles of the ipsilateral extremity below the lesion (Wagley, 1945). Lippitt (see Hines, 1943) found a differential distribution of the atrophy in the muscles not only of the extremities but also of the trunk contralateral to an area 4 removal of a year's duration in the macaque. Dejerine (1900, p 597) recorded the finding of muscular atrophy in hemiplegia without changes in the ventral horn cells and when rheumatism was not present. Oppenheim (1923, vol. 2, p. 1054) seemed loath to admit that muscular atrophy could be found in some cases of uncomplicated hemiplegia. And Gowers (1893, p. 518) reported a wasting of muscles in similar conditions without spread of a destructive process to the motor nerve cells of the spinal cord, but considered this wasting as due to an irritation in the descending degeneration in the pyramidal tracts. Subsequent to removal of the precentral gyrus Marinesco (1903) listed as atrophic the deltoid, pectoralis major, flexors and extensors of the fingers, adductor of the thumb, retractors of the thigh, and flexors of the knee. Certainly in the writer's experience wasting characterizes the skeletal muscles contralateral to excision of all of area 4 of the macaque, or even of its posterior half (4γ).

Contracture—Contracture or shortening of skeletal muscle was found contralateral to lesions of the precentral gyrus in primates. All muscles opposite the lesion were not shortened, and all contractured muscles were not equally affected. In the clinical literature generalizations such as "the

muscles least paralysed become contractured" or "the muscles showing the greatest tonicity are shortened" attempt to explain the distribution of this condition. So far no one has attempted in man to discover whether all muscles which cooperate to perform a given movement show a similar percentage of shortening.

Since contracture does not follow upon surgical division of the pyramids in the monkey (except in infancy, Tower, Chapter VI) or chimpanzee (nor in Hausman's case), then the corticifugal systems, the loss of which is followed by contracture. do not pass through the pyramids. They are extrapyramidal. Moreover, contracture succeeds the superposition of an area 4 lesion upon a division of the pyramids. So far in man the writer has found but one account of contracture following a partial lesion of the precentral gyrus, that of the flexors of the fingers in Horsley's ablation of the arm area. Such circumscribed lesions offer an opportunity to study the differential in distribution of this condition.

FUNCTION OF THE PRECENTRAL GYRUS AFTER LOSS OF OTHER PARTS OF THE CENTRAL NERVOUS SYSTEM

The method of reading the contribution of function of the precentral motor cortex in terms of the changes which result from its loss is given pause by the consideration of the inability of that cortex to control the sequence and degree of contraction of skeletal muscle without the active participation of the cerebellum (Bailey, Chapter X) and the group of nuclei in the basal plate of the brain stem.

To Bucy (see Chapter XV) the interruption in the circle of neurons which eventually discharge from the ventrolateral nucleus of the thalamus into the precentral subsector is succeeded by involuntary movements. For Benda and Cobb (1942) the neurons whose interruption is followed by tremor of the Parkinson type are the internuncial paths between the cortex and the spinal cord. The synchronization of the action potentials recorded for self-initiated contraction of skeletal muscle of the extremities in tremor (Hoefer and Putnam, 1940) would seem in Bucy's view to be summed at the cortical level and in that of Benda and Cobb at the spinal cord level. It is a question whether or not the discharge of nerve impulses by the corticifugal pathways reaching the ventral horn cells are in themselves similar to the discharge which characterizes the normal individual. Certainly, the corticifugal pathways cannot be reached for direct test, for only the discharges within the muscles themselves have been recorded. Nevertheless, Hoefer and Putnam (1940) found that the electrical rhythm of the motor cortex in individuals suffering from tremor resembled the normal.

Whatever the location of synthesis which results in the normal asynchronous discharge, the removal of that part of the precentral gyrus in which the extremity showing the involuntary movements is represented is succeeded by a loss of the objectionable movements.

Certainly these findings should emphasize anew the interdependence of the central nervous system when read in the use of muscle.

DISCUSSION

The precentral motor cortex, bounded posteriorly by the fissura centralis, dorsally by the sulcus cinguli, anteriorly by the anterior boundary of area 6, and ventrally by the great lateral fissure, is distinguished in man by five cytoarchitectonically distinct areas. Although not separated by clean-cut boundaries, these regions have their own particular contributions to the control of muscle.

The foregoing descriptions have demonstrated that the cytoarchitectural differentiation of the precentral motor cortex can be related in part to the type of loss which succeeds the ablation of its discrete parts. Removals of areas 6, 4s, and 4γ in the monkey were found to be followed by losses which were as characteristic as the cellular arrangements which characterized the parts. Area 4s in the chimpanzee was found to behave in a manner similar to the homologous region in the macaque, for strychnine applied to its surface suppressed activity as recorded by the oscillograph in other parts of the cortical surface (McCulloch, Chapter VIII). In man removal of the subdivision of area 4γ, for the lower extremity, without involving area 6, was followed by spastic paralysis. However, it should be noted that in man the "leg" area is not divided into area 4γ, 4a, and 4s as distinctly as is the "arm" area, and that in some parts of the "leg" area, area 4a is absent and area 4γ overlaps area 4s (see Chapter II). But in the subdivision for the upper extremity within the precentral gyrus of man, a phylogenetically new architectonic field was found, 4a (FA, von Economo and Koskinas). Kleist described, as a result of loss of this region (known to him as 6aα), a condition of "apraxia of movement and rest." Although this region is always removed in ablations of the arm area, no description of sequelae to this operation has materially differed from those which follow removal of area 4 in the macaque.[16]

Although no radical difference was found to exist in the cellular architecture of area 6 among the primates Bonin studied, nevertheless the

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[16] This statement may not be true, because the results of lesions in man have not been studied with an attempt to discover exact losses in skilled movements which require simultaneous grading of innervation between prime movers and antagonists and quick shifts in initiation of movement between proximal and distal groups of muscles.

results of excision appear to be more debilitating in man than in the other primates. No topographical localization has been found, but in the monkey inhibition of the grasp was more effective from its anterior division, and that of tonic flexion from its posterior.

Strict somatotopical localization appears to be abrogated by the results of electrical stimulation of the precentral gyrus of man as given by Penfield and Boldrey (1937) and to be restored in large part by the latest analysis from Penfield's clinic (Rasmussen and Penfield. 1947). Nevertheless, the sequelae of removal of small parts of this gyrus as reported by Penfield and Erickson (1941) prove that topical localization must be present. For laboratory primates no such discrepancy exists. With care and luck the impairment of self-initiated movements which results from ablation of an electrically determined part is confined to that part.

Recent results of stimulation of the precentral gyrus in primates fall naturally into four groups, contraction of single muscles or parts of muscles. the elicitation of parts of progression patterns. the innervation of either extensor or flexor sheets of muscles, and the elicitation of use patterns. Removal of this region is followed by the loss of innervation of single groups of muscles, certain use patterns no longer appear, and the utilization of parts of progressive movements and that of parts of extrapyramidal patterns of extension and flexion is lost. On the other hand the differential loss of isolated movements was found both distally and proximally, and did not correspond directly with the size of the cortical area which yielded these movements. "Isolated" retraction of the thigh and "isolated" adduction of the thumb suffered equally. The larger area of cortical representation seemed to be associated with the frequency of movement peculiar to the animal rather than with the severity of paralysis occasioned by ablation. Thus, although extension of the knee was reported as resulting from more points on the precentral gyrus of man than flexion of that joint (Foerster, 1936b), the flexors of the knee have been reported as taking the greater loss. Corticalization of movement, in the strict sense then. cannot be read alone in the differential distribution of paralysis.

In view of the findings of Woolsey and of Chang. Ruch, and Ward that the contraction of the muscles of the extremities. elicited by stimulation of the precentral gyrus with the electric current. can be projected upon the "arm" and "leg" areas in a definite pattern, is it not legitimate to reconsider Hughlings Jackson saying that "nervous centers know nothing of muscles, they only know of movements," and Sherrington's conclusion that movements, not muscles. are represented in the "motor" cortex? Movements are the result of contraction of muscle. either as isolated organs or as functional units. Since it is possible to elicit contraction of

single muscles by electrical stimulation of the "motor" cortex with certain types of current, there must be a nervous pathway which carries the impulse from the cortex to a motor nucleus within the brain stem or spinal cord. May we not consider that ability to select the prime movers depends upon a mosaic of cortical cells of origin of corticifugal systems within the precentral gyrus, and that the axons of these cells have direct anatomical relation to motor nuclei of the lower neural axis? For example, it is possible by electrical stimulation of a point on the macaque's precentral gyrus to produce extension of the thumb, a contraction of the extensor pollicis longus (there is no extensor pollicis brevis in the macaque). If the monkey resembles man, he does not in life extend the thumb without action of other muscles, for Beevor (1903) has observed that the human does not extend the thumb without action of the extensor and flexor carpi ulnaris. On the other hand, man and monkey are able to ulnar flex the wrist, using the extensor and flexor carpi ulnaris as prime movers. The ability to select a single muscle as a prime mover is limited, however, to joints which are moved by contractions of single muscles. And there are few of them! If the idea of representation of muscles (see Fulton, 1938) is too strong a meat to be assimilated within the body of our thought, let us acknowledge that movements as contraction of single muscles can be demonstrated by electrical stimulation of the surface of the precentral gyrus.[17, 18]

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[17] Let the reader make no mistake about this conclusion There is a difference between the discrete topographical projection of striated musculature upon the precentral gyrus of primates, as determined by excitation of contraction of muscles and the ability of the intact animal to utilize his muscles in the performance of movements. This difference is particularly evident when the maturation of excitability of this region in the macaque (Hines and Boynton, 1940) is compared with the development of so-called discrete use of musculature in the infant of this species (Hines, 1942)

[18] (As much has been made of this question of the representation of muscles or movements in the motor cortex, the editor would like not only to agree fully with the above discussion and footnote (17) but also to draw the reader's attention to the fact that although the intact neuromuscular mechanism produces movements which are the result of the coordinated activity of varying combinations of muscles, and is not commonly capable of producing contractions of a single muscle or part of a muscle, that does not exclude the possibility that individual muscles and even parts of a muscle are represented in some one part of that neural mechanism The spinal cord is a part of that intact neuromuscular mechanism No one would deny that single muscles or parts of a muscle are represented there, even though that spinal cord in the intact animal is not able to produce isolated contractions of those small muscular units The same applies to the precentral gyrus As Dr Hines has noted, all existing evidence obtained both by excitation and destruction indicates that isolated muscles, even parts of a muscle, are represented in area 4γ of the precentral gyrus It is likely that the muscular units innervated by a single cell there are larger than the muscular units innervated by a single anterior-horn cell. In the light of modern knowledge, there is no reason for denying the representation of single muscles in the precentral gyrus if one is concerned with the manner and mechanism of the cortical control of movement If one is concerned only with the activity of the intact animal, and not with how that activity is achieved, it may be defensible to talk of the cortical representation of movement and deny the representation of muscles in the nervous system as a whole But if such be one's attitude he is not interested in the problems of intricate structure and function which have concerned the authors of the monograph and which have been the subject of their researches—FULTON.]

From all the data in hand, removal of the precentral gyrus is succeeded by loss of ability to select the desired prime mover or prime movers. But this loss does not affect all muscle groups alike. In stepping forward (bipedal, monkey) the protractors of the thigh are capable of leading off; in stepping backward, the retractors do not palpably contract. After small discrete removals of the hand-finger area, the flexors or the extensors of single digits cannot become prime movers for years of training, and yet as a whole they are capable of that activity. This loss of ability to choose the prime mover is differential, selecting some muscles or groups of muscles for complete loss, others for a partial loss, and still others for a loss apparently only in the degree of their power of contraction.

Besides this selective control of movement exercised by the contralateral precentral gyrus, determined by loss sustained by its removal, there seem to be two other losses both of which seem to be non-topical. The greater the loss of this cortical area, the greater the difficulty of controlling the movements which survive. This effect appears to be exercised both contralaterally and bilaterally. The other is the reciprocal of the first—a small remnant of area 4 (in the macaque) left behind after removal of the rest of the representation of all four extremities seems capable of bestowing a greater ease in innervation on all musculature opposite to the remnant, whatever type of body representation may be contained therein. (The face area is excluded from this generalization.)

Foerster (1936b) allocated ipsilateral innervation which he obtained by stimulation of the precentral gyrus to the ipsilateral corticospinal fibers. Penfield and Erickson offer no explanation because they were never able to cause ipsilateral movements of the extremities by stimulation of this region of the human cortex. In the macaque, Tower and Hines (unpublished) have observed that ipsilateral contractions of muscles of the extremities elicited by stimulation of this cortical area survived section of the ipsilateral pyramid. Nevertheless, an ipsilateral tract having its origin in area 4 and passing through the pyramids is present in the lateral funiculus of the macaque. Degenerated myelin can be followed in Marchi preparations into the gray matter of the same side, passing toward the dorsal horn, into the intermediate area, and lying among the cells of the ventral horn. Further, in similar preparations made in the writer's laboratory of a gorilla's cord, subsequent to removal of the leg area by Dr. J. F. Fulton, small amounts of degenerated myelin were observed to be present in homologous regions not only of the lumbar and sacral levels of both sides but also in those of the cervical cord and thoracic regions chosen. For the time being, may not the possibility be considered that the ipsilateral fibers of the corticospinal tract might possibly partake in the innervation of the cooperating extremity; and the contralateral fibers entering the cervical

and thoracic levels as either facilitating movement or fixation? Such a consideration would not conflict with the fact that the electric current applied at the cortical level has not revealed their activity as the initiation of movement.

Moreover, the ablation of the precentral gyrus is also followed by differential incidence of other phenomena. There is a selective distribution of hypertonus, one of contracture, and another of atrophy. Of these, only the atrophy followed surgical divisions of the pyramids. Moreover, since wasting of skeletal muscle also was found subsequent to interruption of the ventral division of the lateral funiculus in the spinal cord, atrophy may be allocated not only to the loss of corticifugal systems which pass through the pyramids but also to that of extrapyramidal systems as well. On the other hand, the degree and distribution of contracture followed cortical loss of extrapyramidal systems, in the presence of severe pyramidal defect in the monkey, and therefore related in part only to the degree and distribution of hypertonus. For not all hypertonic muscles are contractured and not all contractured muscles are hypertonic. Nor does the distribution of "the least paralyzed" muscles coincide with that of contracture. In other words, at the present time there is no common denominator for the selective incidence of atrophy, hypertonus, and contracture.

The assay of the phenomena of release associated with the hypertonus which succeeds lesion of the precentral gyrus depends upon the reaction of skeletal muscle to stretch. Consequently clonus and brisk tendon reflexes should also be characteristic of those muscles which show the "clasp-knife" type of resistance to passive movement. In the writer's experience all hypertonic muscles show brisk tendon reflexes, but brisk tendon reflexes are not confined to muscles which are hypertonic. And all brisk tendon reflexes do not irradiate. Clonus also has its own selective distribution. Furthermore, the resistance to passive movement which characterized the monkey's flexors of the elbow in the sitting posture shifted to the extensors of that joint when made to support the weight of the body on the upper extremity, resembling a condition in certain hemiplegics which Brain (1927) has called the quadripedal extensor reflex. This shift from the upright to the prone posture in the monkey did not affect the hypertonus of the wrist flexors, any more than it did that of the ankle flexors (i.e., plantar flexors).

During the spastic state of development in the infant macaque (Hines, 1942) the regression of hypertonus, of brisk tendon reflexes, and of their irradiation did not occur at the same rate nor at the same time even in muscles in which they had been simultaneously observed. Clonus was never obtained as a response to the usual stimuli.

Although it is difficult to believe that the results of these several methods of assaying the response of skeletal muscle to stretch reveal the presence of separate corticifugal pathways for each of them, Wagley's analysis of spasticity produced by lesions of the spinal cord (macaque) suggests that there may be more than one. Certainly, the degree of hypertonus increases when more extrapyramidal pathways are interrupted at the cortical level, and its quality and distribution have been shown to be affected by the removal of cytoarchitectonically discrete cortical areas.

The whole area frontalis agranularis in the macaque presents a double organization of extrapyramidal activity. Its anterior division has assumed the activation of the least stereotyped extrapyramidal action and a control of tone, unassociated with the pyramidal system. Electrical stimulation of area 6 produces complex reaching and grasping acts and inhibits tonic flexion and releases the grasp; whereas, that of the anterior border of 4 (4s plus) and annectent 6 produces diagonal movements used in progression and inhibits standing tone. When the pyramids are divided electrical stimulation of the posterior division of the area frontalis agranularis is able to produce complex movements of all four extremities as well as release of their tonic extension. Both the motor and inhibitory action which characterizes the extrapyramidal systems which stem from the whole precentral subsector of the macaque's cortex cerebri is non-topical.

In man evidence for similar activity of extrapyramidal systems is incomplete. Although Foerster is the only neurosurgeon who has elicited extrapyramidal movements by stimulation of area 6, the results of lesion in this region suggest that inhibitory action against tone is present. That the anterior border of area 4 may have a function similar to that described for the macaque is suggested by decrease in resistance to passive movement elicited from the homologous region of the human cortex (Bucy and Garol, 1944). The functional contribution to the control of movement made by the extrapyramidal systems which stem exclusively from area 4 in man has yet to be analyzed. The comparison of results of the suspected lesion to the pyramids in man (Tower, Chapter VI) with those of the other primates studied indicates that in the human, as well as in the ape and monkey, the remaining corticifugal systems display mass organization only. The extrapyramidal motor and inhibitory systems which survive fail to confer upon the pyramidal preparation ease of initiation of movement, facilitation, adjustability, and modification during the progress of its execution. No longer is such an individual primate capable of the finer varieties of usage of skeletal muscle.

The discrete organization of area 4γ remains a mooted question for some commentators in spite of the fact that it is possible to analyze its

basic plan in terms of reacting muscles. No common denominator has been found for the results which follow ablations of this cortical surface in man (compare Foerster, Bucy, Penfield and Erickson). Indeed, the control of use of skeletal muscle which has been observed to persist after such lesions has been explained (1) as the result of activity of the ipsilateral pyramidal tract (Foerster, 1936a, b; Bucy, Chapter XIV), and (2) as evidence of multiple representation of movements within this cortical area (Hughlings Jackson; Walshe, 1946). Certainly, if multiple representation within the precentral gyrus of the macaque exists the bilateral loss of the leg area should not reduce the lower extremities to the status of support only. Indeed, the intactness of both arm and both face areas is unable to confer upon the animal the hand-like use of the foot so characteristic of the monkey's activity. Indeed, wisdom dictates that assignment of the control of movement which survives lesions of area 4γ to any particular organization within the posterior division of the precentral subsector be postponed until the function of a second motor area found within the operculum of the frontal lobe is analyzed. Bailey (1947; personal communication) found that this second motor area has a reversal of topical localization similar to the reversal found within the second sensory areas which characterize each of the three posterior lobes (somatic sensory areas I and II, Woolsey and Fairman, 1946; auditory areas, Walzl and Woolsey, 1943; visual areas, cat, Talbot, 1942).

The differential distribution of "paralysis" observed in man after capsular lesions and after removal of the precentral gyrus in laboratory primates awaits further analysis. We do know, however, that the monkey's ability to step (bipedal) forward and lateralward after bilateral ablation of the arm and leg areas vanishes if area 6 is added to the initial lesion; and that the mass innervation of the musculature of the extremities which enables the bilateral 4 and 6 preparation to maintain posture (abnormal to be sure) to initiate quadripedal progression (also in an abnormal way) and to feed itself (use of musculature, synergistic) also vanishes after the remaining prefrontal areas are removed. No one has assigned to these areas control of the movements which disappear when they are added to the initial lesion. This suggests that reactivity of muscle to the electrical current is of major importance in our allocation of control of skeletal muscle to the cortical surface of the frontal lobe.

The discrete use of skeletal muscle and the ability to fix muscles not so used are intimately related both functionally and anatomically for they disappear together when the corticospinal system is radically injured. The development in time of these two aspects of use of skeletal muscle in the infant macaque suggests that the ability to fix musculature (trunk, girdles,

and proximal in the extremity) frees distal musculature for discrete use, for the adult type of discrete use of distal musculature does not appear until the ability to fix proximal musculature has matured. There seems to be a further intimate anatomical relation between musculature used in these two ways. For as long as coinnervation of muscles of the trunk and those of the girdles persists, and as long as the contraction of proximal muscles which move the extremity into position, preceded by a short interval of time the innervation of distal musculature, is observed in the infant's performance, similar coinnervations and visible fixations can be evoked by the electric stimulation of the precentral gyrus in the infant monkey. When these two phenomena ceased to play a visible role in performance they were no longer elicited (Hines and Boynton, 1940). In some mystifying manner their sublimation was complete. These findings suggest that the results of small lesions of area 4γ may be read not only in terms of "paralysis" of some muscles but also in those of freeing others, so that they contract visibly rather than perform their function of invisible fixation.

In conclusion, the significance of the precentral motor cortex lies in its ability to confer upon the individual who possesses it within an intact nervous system the discrete use of skeletal muscle directed toward a given end. The ability to direct this discrete control of skeletal muscle is quite possibly the contribution of the anterior division of the area frontalis agranularis; the execution of that control is most assuredly that of the posterior division of that area. The discrete control exercised by the posterior division is dependent upon the organization of the corticospinal system which stems from the precentral gyrus. This complex descending system contributes "to the central excitatory state of the segmental motor mechanism" and seems to lend to phasic activity an ease of initiation as well as a certain grading of contraction. Moreover, the ability to control skeletal muscle for discrete action is dependent upon the cortical organization of the whole precentral subsector; upon that within its anterior division for mobility in tonic innervation, and upon that within its posterior division for selective fixation of musculature as well as for selective phasic activity.

This phasic activity appears to be initiated as a choice of innervation either of a single muscle (when the chosen joint is moved by a single muscle, see p. 492) or of a group of muscles. This initiation of contraction (i.e., innervation of prime mover or of prime movers) is always accompanied by that of cooperating muscles, by fixation of more proximally lying muscles, and by graded contraction or relaxation of antagonists. In skilled performance directed to accomplish a given end, the "fusillade"

innervation of the cooperating extremity is as important as the innervation of the active or leading extremity. This cortical tissue makes possible stopping a movement at a given degree of contraction, and starting it again at a degree of contraction necessary to follow through to the desired end easily and without effort. Stereotyped patterned movements, integrated at lower levels can be utilized as parts or wholes. Postural patterns can be assumed, modified and shifted such that an undetermined move can be made easily and instantly. To be "on his toes" is more than a trite expression.

Posture must not only be maintained in an easy, natural way to free the hand for manipulation, but must also anticipate by its adjustments the next movement. Exquisite as the movements of the fingers are, they do not work alone. And the variants in cooperation of movement, in fixation and in the increment and decrement of tone of muscles of the trunk, of those which attach the extremities to the girdles, and of those of the proximal part of the extremities are as important as movements of the digits in the attainment of skilled movements. No violin or piano was ever played with the fingers and hand alone.

The precentral motor cortex is not an isolated piece of nervous tissue sending out its impulses to lower motor centers. Its accomplishments are dependent upon the intactness of its thalamocortical relations. The instant obedience of muscles demanded in the performance of skilled movements is dependent upon intactness of other parts of the nervous system, in particular that of the basal ganglia and the cerebellum. The nice modulation of movement requires relation of this tissue to other cortical areas. The precentral motor cortex reaches out to construe cooperation of its mirrored counterpart; it requests the contribution of the postcentral gyrus via fibers which run beneath its posterior boundary. It receives modifying impulses from all the somaesthetic sectors of the parietal lobe.

The aim which the skilled performance realizes is not an achievement of the precentral motor cortex alone; for the interpretation of distance, and the meaning of the object manipulated and even a part of the control of the manipulation itself is the contribution of sight. Motor adjustments are not made in theoretical space; they are made relative to an object within reaching distance, within stepping distance, and within one made out of interpretation of distance as translation through space. Examination of an object by manipulation follows its possession, determined in turn by the ability to fix and converge the eyes upon the object seen. Movement can be modulated by yet another sense, hearing. Long association fibers with its areas of association are dense enough to be picked up by our crude methods of degeneration.

But the end of the skilled performance may not be in view. To achieve it, skilled movements may have to take place in successive stages, both in space and in time. Here the prefrontal areas make their contribution.

The precentral motor cortex is not an isolated sheet of nerve cells. Rather, through its intercortical and subcortical relationships it becomes the chief executor of the cerebral mantle. Its intactness confers upon us the ability to express the increment of our slowly and sometimes painfully achieved education. Without this region of the cortex cerebri we would be able to move, but we could not "change our minds" in the middle of a movement. Without this cortical tissue we would not have such rapid and easy initiation of contraction of the muscles of our choice or the almost instantaneous stopping of that contraction. Indeed, the facile grading of the degree of contraction and the ready shifts of tone to fit the purpose of the act would be lost. We do not know exactly how the precentral motor cortex produces this miracle of control of movement; but there it is, awaiting further analysis.

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Explanatory Note

Authors and publications mentioned in the text are listed in the Bibliography, pages 501-550, and generally are not repeated in the index; entries are made under an author's name only in the instances where his work is quoted or discussed.

Numbered areas of the cerebral cortex are set in italics in the index to distinguish them from page references, although they are not italicized in the text.

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